CEREBROSPINAL FLUID ENZYMES IN ACUTE NEUROLOGICAL EPISODES

THESIS

FOR DOCTOR OF MEDICINE

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CERTIFICATE

This is to certify that the work embodied in this thesis has actually been carried out by the candidate himself. He has also put in the necessary stay in the department of Medicine as per University regulations.

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C E R T I F I C A T E

This is to certify that the work entitled "CEREBROSPINAL FLUID ENZYMES IN ACUTE NEUROLOGICAL EPISODES" which is being submitted as a thesis for M.D. (Medicine) by DR. MADHUKAR MISRA has been carried out under my direct supervision and guidance in the Department of Medicine. The techniques embodied in this thesis were undertaken by the candidate himself and the observations recorded have been periodically checked and verified by me.

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INTRODUCTION

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It has long been recognised that disease may increase the outflow of intracellular enzymes from tissues where these are abundant. Measurements of such enzymes have been of unequivocal value in the diagnosis of cardiac, hepatic, renal and muscular diseases.

Diagnostic considerations in the sphere of neurologic diseases are usually derived from pertinent history and physical findings with but limited guidance afforded by laboratory procedures. The classic biochemical techniques used with advantage in somatic diseases have but limited value in the diagnosis of primary nervous system disorders. In recent years the clinical applicability of quantitative enzyme activity in biologic fluids has been explored extensively particularly in relation to hepatic, myocardial and neoplastic substances. Through this avenue of approach, a battery of sensitive tests has been evolved, often with notable diagnostic and prognostic utility. The central nervous system content of Glutamic oxaloacetic transaminase (G.O.T.) is much higher than that of hepatic tissue and almost equal to that of cardiac tissue (Cohen and Nakhuis, 1941; Awapara and Seale, 1952). Lactic dehydrogenase is another such enzyme which is widely distributed in different tissues including nervous tissue.

In neurological disease the rise in C.S.F. enzyme activity depends upon the site of lesion, degree of cellular damage and its accessibility to spinal fluid. The clinical significance of enzymology in most of the nervous system disorders is undecided as yet.

Cerebrovascular accidents constitute about 29% of all neurological disorders (Wadia, 1977). As previously stated, the diagnosis of acute neurological episodes like acute C.V.A. and encephalomeningitides is mainly clinical. It is often not possible to clinically and biochemically differentiate between cerebral embolism and thrombosis on one hand and cerebral haemorrhage on the other. Likewise, in encephalomeningitides the clinical picture and C.S.F. examination are many a time inconclusive and do not give the clinician much scope for exact diagnosis or assessment of prognosis.

Though serum and C.S.F. enzymes have been studied by various workers, yet a clear understanding of their variations in neurological diseases is yet to emerge.

In view of the existing situation in this field, the present study was planned to evaluate the importance of C.S.F. and serum levels of Aspartate transaminase (A.S.T.) or Glutamic oxaloacetic transaminase (G.O.T.) and Lactic dehydrogenase (L.D.H.) in acute cerebrovascular accidents and encephalomeningitides.

AIMS OF STUDY :

1. To determine serum and C.S.F. Lactic dehydrogenase and Glutamic oxaloacetic transaminase levels in patients suffering from acute neurological episodes (acute C.V.A. and encephalomeningitides) and in normal controls (persons undergoing spinal anaesthesia for operation of piles, hydrocele and varicocele and having no disease likely to affect the level of transaminase and lactic dehydrogenase).

2. To determine to relationship of serum G.O.T. and L.D.H. levels and C.S.F., G.O.T. and L.D.H. levels in acute neurological episodes.

3. To study the application of these enzyme levels in C.S.F. and serum in the evaluation of acute neurological disorders and in estimating their progress and prognosis.

4. To study the application of these enzyme levels in C.S.F. and serum in the differential diagnosis of the acute neurological episodes being studied.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

INTRODUCTION :

The determination of the enzyme activity has a wide range of application. In addition to the testing of enzymes used as reagents for the analysis of substrates, enzyme assays are of special importance in the biochemical and clinical fields. The concept, that certain disease states can be detected by altered enzyme activity in serum and C.S.F., rests upon a number of assumptions. Intracellular metabolism is essentially a collective chain of successive biochemical transformations, each mediated by highly specific biologic catalysts. The continuance of cell life is dependent upon uninterrupted activity of these agents. Destruction or serious physiologic impairment of selective tissues may, therefore, liberate the intracellular enzymes into the most readily accessible biologic fluid. The relative concentration of various enzymes in all cells varies according to their metabolic specialization. According to Delbruck et al (1959), it is possible to distinguish approximately three types of enzymes according to their location in the cell.

1. Cytoplasmic enzymes (e.g. lactic dehydrogenase).
2. Enzymes located only in the mitochondria (e.g. glutamic dehydrogenase).
3. Enzymes which occur in both cell compartments, (e.g. glutamic oxaloacetic transaminase and malic dehydrogenase).

The intracellular enzymes have hardly got a role to play in the serum or cerebrospinal fluid. These include the enzymes of tissue metabolism, and they are not active in serum or cerebrospinal fluid because their coenzymes and most of their substrates are absent in the serum or cerebrospinal fluid. The majority of the enzymes in this group, which have been studied from a clinical stand point, belong to the main energy yielding metabolic pathways i.e. they are present in all tissues of the organism. It can therefore well be assumed that whatever enzyme activity is found in such circulating fluids, denotes the enzyme in transit from cells and that the source of these enzymes is probably a combination of continuing intracellular biosynthesis and normal cell replacement.

The rise in the circulating content of a specific enzyme can be construed as a signal of necrobiosis or functional damage in such tissues. The localisation of the responsible tissue is not always feasible but with judicious evaluation of relevant clinical data, a reasonable guess can be made. It is also possible at times, to infer the nature of the pathologic process.

An abnormally increased serum or cerebrospinal fluid enzyme activity in most instances indicates a release from pathologically altered cells, rather than enhanced biosynthesis.

It can be shown under experimental circumstances that the enzyme increase in the circulating fluid is

closely associated with decreasing tissue enzyme levels (e.g. induced myocardial or cerebral infarctions in laboratory animals). The serum enzyme returns to normal as experimentally induced tissue degeneration persists, indicating an exhaustion of the primary source of additional circulating enzyme. Generally, the elevation tends to be transient and the peak values are recorded at the onset of the destructive process. They therefore may not coincide with the time of the most profound tissue damage.

When enzyme activity does show a sustained elevation which is rare, it often presages a continuing cell degeneration, progressively incorporating previously unaffected tissues. Serial measurements of enzymatic activity therefore have a definite bearing upon the prognosis, serving to indicate the quantitative extent of acute tissue damage, (by the magnitude of initial peak in enzymatic activity) and extension of the destructive lesion (by the endurance of abnormally elevated enzyme activity). (Aronson et al, 1960). Like all laboratory parameters, the information derived from measurement of body fluid enzyme activities has noteworthy limitations. Majority of enzymatic reflections are nonspecific, in that more than one etiologic factor and more than one anatomic site can account for similar quantitative and/or serial enzyme changes. Furthermore, the influence of other body fluid constituents such as inhibitors, antienzymes, activators, competitors, drugs and others may account for

apparent artefacts included in the extensive enzyme activity of body fluid (Wroblewski, 1959).

There are more than five hundred enzymes whose catalytic function has been described, but only a small number have been used as indicators of neurologic disease states. The studies of altered enzyme activity have been confined principally to the cerebrospinal fluid.

1. C.S.F. ENZYMES :

A knowledge of the cerebrospinal fluid (C.S.F.) enzymology may lead to a better understanding of the physiology of the central nervous system. It mayalso aid in the clinical evaluation of the diseases of central nervous system.

The first attempts to investigate the relationship between the condition of central nervous system and the distribution of enzymes in C.S.F. date as far back as 1938 when Kaplan et al estimated activity of Trypsin, Phosphatase, Lipase tributyrinase, Esterase and Amylase in the pathological as well as normal spinal fluids. Bucher in 1952, found an increase in triosephosphate isomerase in C.S.F., in cases of cerebrovascular accidents. In malignant brain tumours; phosphohexoisomerase activity was found to be increased in the C.S.F. by Thompson in 1959. Various other enzymes have been found to act as biochemical markers of diseased central nervous system. Creatine Phosphokinase (C.P.K.) is one such enzyme. The

importance of evaluation of C.P.K. has been realised in many neurological disorders. (Herschowitz and Cumings, 1964; Lisak and Craig, 1967). Besides C.P.K. other enzymes which have been studied in the C.S.F. include Deoxyribonuclease and Ribonuclease (Kovacs, 1954; Mouch, 1958), cholinesterase (Jefferson, 1954; Plum and Fog, 1960) and Glutathione reductase (Manson and Wroblewski, 1958).

Lactic dehydrogenase (L.D.H.) :

This is an enzyme of almost universal distribution in the body which catalyses the reversible transformation of pyruvate to lactate. This is found in most animal tissues, besides in body fluids such as serum, serous effusions, urine, and cerebrospinal fluid. Heart, liver and skeletal muscle in particular, contain large amounts of the enzyme. Brain tissue contains per gram about one third the L.D.H. present in liver. When the blood brain barriers are intact C.S.F. - L.D.H. is not altered by ten fold higher plasma L.D.H. activity. The fluctuations in plasma L.D.H. also have no effect on that in C.S.F. (Wroblewski, 1958).

L.D.H. of the human tissues contains five distinct isoenzymes. Different tissues vary in the relative proportions of these five isoenzymes. Heart muscle contains mainly the electrophoretically faster fractions 1 and 2 and so do plasma, C.S.F. and brain tissue. Skeletal muscle contains mainly the slower fractions 4 and 5 like granulocytes, and liver contains mainly fraction 5.

In disease the serum isoenzyme pattern approaches that of the affected organ and the pattern may remain demonstrably abnormal even after the total enzyme activity has reentered the normal range.

Glutamic oxaloacetic transaminase (G.O.T./aspartate aminotransferase) :

This is one of the transferase group of enzymes. It's systemic name is L Aspartate 2 oxoglutarate aminotransferase. This enzyme is involved in the following interconversion :

L Glutamate+oxaloacetate⇌L Aspartate+(alpha) oxoglutarate.

It has been detected in microorganisms and in all human and animal tissues so far investigated. In humans, the richest source is heart muscle, followed by brain, liver, gastric mucosa, adipose tissue, skeletal muscle and kidney etc. Body fluids like serum and C.S.F. contain it in substantially smaller amounts. (Bergmeyer and Bernt, 1965).

Source of enzymes in C.S.F. :

Controversy still exists as to the source of C.S.F. enzymes. Though brain tissue contains substantial amounts of L.D.H. and G.O.T., yet it still remains an enigma whether these C.S.F. enzymes are of cerebral origin or reach the C.S.F. from the plasma after crossing the blood brain barrier. Besides brain and plasma, two other possible sources have been postulated. These are the leucocytes and the microorganisms. It must be noted

however, that the possible source in a given diseased state varies according to the pathophysiology involved. For example, in cerebral infarctions, the sources which might be responsible for the enzymatic activity, in the C.S.F. can be either cerebral tissue or plasma, but never microorganisms or leucocytes. The reverse holds true for inflammatory diseases of the C.N.S.

In cerebrovascular accidents, frank infarction is presaged by cellular damage. Cellular damage takes place in all the varieties of the cerebrovascular accidents viz. thrombosis, embolism and haemorrhage.

The level of G.O.T. in C.S.F. at any moment depends on its rate of entry and its rate of removal. There could be several ways for a rise in C.S.F., G.O.T. activity. (Mellick and Bassot, 1964) e.g. :

1. Increased outflow from serum through an incompetent C.S.F./blood barrier.
2. Increased out flow from cells because of their destruction.
3. Increased outflow from cells in absence of their destruction.
4. A decreased rate of removal.
5. A continuation of some or all of these factors.

The size of the infarcted area has an important bearing upon the rise in the enzyme activity. (Brodeli et al, 1959). Wilcock et al in 1973 reported that in normal brain, plasma is the source of C.S.F. L.D.H. and G.O.T.

They did not find any contribution for the same from the brain tissue. While others (Maas, 1977 and Viallard et al, 1978) reported on the basis of isoenzyme studies that the increment in C.S.F. enzymatic activity was of cerebral origin.

Beaty et al (1968) reported predominance of L.D.H. fractions 4 and 5 in C.S.F. in cases of bacterial meningitis, thus proving their origin from leucocytes. Interestingly, however it was found that in fatal cases of bacterial meningitis, the C.S.F. showed predominance of L.D.H. 1 and 2, consequent to extensive damage of brain tissue.

Acute cerebral damage leading to release of G.O.T. from brain cells and raising serum enzyme activity has been reported by Lieberman, (1957). There are several workers viz. Hsieh and Blumenthal, (1956), Jakoby, (1958), Green, (1958), Wolintz, (1969) and Wroblewski, (1958) who have attributed the raised C.S.F. enzyme activity to brain tissue. Working on viral cerebral infections Krogsgaard and Quaade (1963) reported neuraxis to be the source of C.S.F. enzymes.

The blood brain barrier may be the deciding factor for the alteration in enzymatic activity of C.S.F. by regulating the passage of leucocytes and/or bacteria and/or plasma, in conditions of diseased nervous system. Plasma may reach C.S.F. in conditions affecting blood brain barrier (Kaplan, 1938). In cases of meningitis,

leucocytes too may contribute, along with the plasma, in raising C.S.F. enzyme activity as reported by Wroblewski (1957, 1958) and Green (1958). Feldman (1975), interpreted that the level of C.S.F. L.D.H. activity reflected the type and number of white blood cells and the kinetics of white blood cell turnover involved in the host response to infection. Similar results have been reported by Aronson (1960), Beaty et al (1960) and Shirole and Nair (1974).

In central nervous system infections, microorganisms could be yet another source of C.S.F. enzymes. (Aronson, 1960 and Shirole and Nair, 1974). On the contrary, Beaty et al in 1968 ruled out the microorganisms as a possible source of enzymes in C.S.F. in meningitis. Their study was based on their observations on leucopenic and normal animals affected with pneumococcal meningitis. Though both group had a large number of viable organisms in the C.S.F., only the group with normal leucocyte count showed a rise in C.S.F. L.D.H.

2. <u>NORMAL VALUES OF G.O.T. AND L.D.H. IN C.S.F. AND SERUM : C.S.F. = G.O.T. :</u>

Though the value depends chiefly on the methodology adopted, most of the workers have reported C.S.F. G.O.T. levels within the range of 5-20 units e.g. (Myerson et al, 1957; Brodall et al, 1959; Aronson, 1960; Landing et al, 1961 and Pradhan and Saxena, 1965 etc.). Some workers have

however reported higher values up to 25 units e.g. Lieberman et al (1957), Singh et al, (1972), Kohli et al, (1978) and Gupta et al, (1982).

S.G.O.T. :

Lieberman et al, (1957) and Myerson et al, (1957) observed double transaminase activity in serum as compared to C.S.F. in their normal controls. No such relationship has however been obtained in diseased states. Most of the workers like Lieberman et al, (1957), Myerson et al, (1957), Brodell et al, (1959), Pradhan and Saxena, (1965) and Singh et al, (1972) have reported S.G.O.T. values ranging between 10-40 units in normal controls. Gupta et al, (1982) have however reported higher values (up to 150 units).

C.S.F. L.D.H. :

In healthy controls the activity of this enzyme has been found in the range of 10-40 u. according to reports available in the literature (Wroblewski et al, 1957; Aronson, 1960; Cunningham et al, 1965; Feldman et al, 1975 and Bedi et al, 1974).

Serum L.D.H. :

Wroblewski et al, (1957) reported control values of serum between 200-680 u. Aronson, (1960), found the normal range between 100-600 u. Wolintz et al, (1969), reported 150-350 u. as the normal range of serum L.D.H. activity. Bedi et al, (1974) observed their control cases to have

S.L.D.H. levels in the range of 76-390 u.

3. ALTERATIONS OF C.S.F. ENZYMES (L.D.H. AND G.O.T.) IN DISEASE :

Cerebrovascular accidents :

The central nervous system is bathed by the cerebrospinal fluid and hence, the examination of this biological fluid should provide relevant information regarding brain damage.

(a) Experimental :

Cohen and Helkhuis, (1941), reported that dry brain tissue contains 260u/mg. of G.O.T. activity. Various workers have studied C.S.F. G.O.T. by producing brain damage under experimental conditions (Waksm and Fleischer, 1965; Smith et al, 1960; Akeshi, 1966). All of them have reported raised activity after producing cerebral damage. However, Khun in 1974 described only slight increase of C.S.F. G.O.T. after producing cold injury in cats.

Green in 1958, observed that L.D.H. might be slightly superior in reflecting tissue damage; both in the incidence of abnormality and in the degree of increase. Akeshi, (1966), Rasmussen and Klatsc, (1960) and Co et al, (1976) have substantiated the rise of C.S.F. L.D.H. in cerebral damage under experimental conditions.

(b) Changes in activity of G.O.T. and L.D.H. :

The enzyme activity in C.S.F. and serum has been measured by various workers by utilising different techniques. The results should then, only be interpreted if due consideration is given to the methodology used.

43% of cases reported by Lieberman et al in 1957 depicted a rise in S.G.O.T. A substantial increase was found only in clinically severe cerebrovascular accidents. Fleisher et al reported only moderate increases in serum and C.S.F. G.O.T. in humans in the same year. Myerson et al. (1957), Mathur et al. (1965), Singh et al. (1972) and Kaul et al. (1978) too have showed similar S.G.O.T. increments.

Mellick and Bassett in 1964 postulated that cortical or subcortical involvement might be expected to show a greater increase than those with more discrete vascular lesions. Rise in C.S.F. G.O.T. in cases of cerebrovascular accidents has been reported by various workers (Green, 1957, 1958; Lieberman et al, 1957; Mathur et al, 1965; Pradhan and Saxena, 1965; Rama Rao, 1965; Singh et al, 1972; Kohli et al, 1978 and Kaul et al 1978.

On the contrary Katzman et al, in 1957 found little correlation between the pathologic process, severity of the disease and the transaminase activity of the spinal fluid. Myerson (1957), reported minimal elevation in only two of his patients.

In 1970, Davies Jones could not detect any rise of C.S.F. G.O.T. in cerebrovascular accidents. He attributed this to delayed C.S.F. examination (more than 5 weeks after the episode) and cases of transient-ischaemic attacks which were present in his series of patients.

No correlation has been found to exist between S.G.O.T. and C.S.F. G.O.T. in cerebrovascular accidents as reported by Brodeil et al. (1959), Mathur et al. (1965), Pradhan and Saxena, (1965) and Rama Rao, (1965).

Rise in C.S.F. L.D.H. in cases of cerebrovascular accidents has been noted by Wrobleswki (1957, 1958), Green et al. (1958), Jakoby and Jakoby, (1958), Cunningham et al. (1965), Wolints et al. (1969), Nelson et al. (1973), Bedi et al. (1974) and Chaudhari et al. (1976). None of the investigators found a rise in serum level of L.D.H. except Lowenthal, (1961) and Chaudhri et al. (1976). Jakoby and Jakoby contended in 1958 that increased L.D.H. levels are not caused by leakage from anoxic brain but rather are a function of repair mechanisms. Wrobleswki in 1958, observed that cerebral haemorrhage without bleeding into the space might either do not alter the enzyme activity or may cause slight increments up to only 75-100 u/ml. He also reported that a communicating cerebral haemorrhage resulted in a sizeable increase in C.S.F.

L.D.H. which later returned to normal. This is due to the contribution of plasma and erythrocyte L.D.H. activities which are 10 and 1000 times higher than C.S.F. L.D.H. activity. Isoenzyme analysis of C.S.F. L.D.H. in cerebrovascular accidents by Cunningham et al in 1965 showed that fractions 2 and 3 were significantly increased.

However, Van Rymenant in 1963, concluded that C.S.F. L.D.H. activity could not aid much in the diagnosis of cerebrovascular accidents. Davies Jones in 1970 also reported normal C.S.F. L.D.H. in cerebrovascular disease. No correlation between serum and C.S.F. L.D.H. levels has been found in cerebrovascular accidents by Wroblewski et al, (1957) and Choudhary et al, (1976). Lowenthal, (1961) reported simultaneous serum and C.S.F. L.D.H. alterations in destructive nervous lesions. The serum enzyme elevations were found to be less frequent and independent from C.S.F. levels (Wolintz et al, 1969).

(c) Diagnostic significance :

In general, maximum levels of C.S.F. G.O.T. have been reported in cerebral haemorrhage (Singh et al, 1972; Kohli et al, 1978, 1981 and Kaul et al, 1976).

While Singh et al reported lowest C.S.F. G.O.T. levels in cerebral thrombosis, S.G.O.T. levels reported by Lieberman et al, (1957) showed equal elevations in cases of cerebral thrombosis and haemorrhage. However,

Laha and Bhargava in 1964 observed that the cause of the accident viz. thrombosis, embolism or haemorrhage per se had no significant effect on the C.S.F. transaminase activity. Kaul et al could not also obtain any critical diagnostic levels.

Working on L.D.H., Green et al in 1958 reported an interesting finding. They obtained highest increments in C.S.F. enzymatic activity in cases of basilar artery thrombosis. No explanation was however offered for the same. As in case of G.O.T., maximum C.S.F. L.D.H. levels have been reported in cases of cerebral haemorrhage (Bedi et al, 1974 and Chaudhari et al, 1976).

(d) Prognostic significance :

It has been supposed thatthe level of enzymatic activity in the C.S.F. and serum could serve as an index of the prognosis. Various workers have reported different enzyme levels to be of prognostic value.

Singh et al, (1972) and Kohli et al, (1978) reported C.S.F. G.O.T. levels above 75u/ml to be of bad prognostic significance. Similar opinion was expressed by Kaul et al, (1978). In 1969, Wolintz et al reported that although some patients with normal or low L.D.H. values did badly, marked elevations were usually associated with grave clinical status and ultimate demise. While no correlation between C.S.F. L.D.H. levels and clinical outcome was possible in haemorrhagic

cases, in non haemorrhagic cases C.S.F. L.D.H. was found to be directly related to the severity of neurological deficit and inversely with the prognosis (Bedi et al, 1974). High serum and C.S.F. L.D.H. levels indicating bad prognosis were also reported by Chaudhari et al, (1976).

Spolter et al, (1962) reported that C.S.F. G.O.T. and L.D.H. levels increased with increasing age and C.S.F. protein concentration, in patients with neurological disorders. Brodell et al, (1959) could not correlate the C.S.F. transaminase activity with C.S.F. protein content or the proximity of the lesions to the subarachnoid space or ventricles. Pradhan and Saxena (1965) and Rama Rao (1965) also did not find any relation of G.O.T. to the levels of C.S.F. protein, chloride or sugar.

Wolints et al, (1969) also could not find any correlation between the magnitude of increase in L.D.H. activity and C.S.F. xanthochromia, erythrocyte count, leucocyte count, or total protein concentration.

<u>G.O.T. and L.D.H. levels in encephalo-meningitides</u> :

Various workers have reported a rise of C.S.F. G.O.T. in acute bacterial meningitis (Aronson et al, 1960; Lending et al, 1964; Reddy et al, 1972; Shirole and Nair, 1974; and Praharaj et al, 1978). The C.S.F. G.O.T. activity tends to be highest in cases of acute bacterial meningitis as compared to other varieties of meningitides.

Reddy et al. (1972) reported a two fold rise in C.S.F. G.O.T. in cases of tuberculous meningitis. The rise in C.S.F. G.O.T. in tuberculous meningitis has also been noted by other workers (Green et al. 1957; Aronson, 1964,; Srivastava et al. 1971).

Praharaj et al reported in 1979 that in tuberculous meningitis, C.S.F. G.O.T. levels were only slightly above the normal. On the contrary C.S.F. G.O.T. has been found to be normal by Shirole and Nair (1974). In encephalitis there is no detectable rise in C.S.F. G.O.T. activity. (Myerson, 1957; Lending et al, 1964; Reddy et al, 1972 and Shirole and Nair, 1974).

The L.D.H. activity of C.S.F. shows a remarkable rise in acute bacterial meningitis. (Wroblewski, 1957, 1958; Aronson, 1960; Lending et al, 1964; Beaty et al, 1968; Neches and Platt, 1968; Feldman et al, 1975; Hallock et al, 1978 and Gupta et al, 1982).

Aronson (1960) has reported there to six fold rise in C.S.F. L.D.H. in acute bacterial meningitis. The value remains normal to low in aseptic meningitis (Lending et al, 1964; Neches and Platt, 1968). While Beaty et al have found slight elevations of C.S.F. L.D.H. in viral infections of nervous system, Gupta et al, (1982) have reported normal levels. Interestingly Feldman, (1975) found significantly lower levels in cases of viral meningitides.

The value is also high in acute tuberculous meningitis (Aronson, 1960; Khanna et al, 1977). C.S.F. L.D.H.

values have been reported to be normal in treated cases of bacterial meningitis. (Lending et al, 1964). However, Hallock et al, (1978) noted that a low or normal level of L.D.H. does not eliminate the consideration of meningitis.

(a) Diagnostic significance :

The level of L.D.H. activity in the C.S.F. of patients with bacterial meningitis might provide a better measure of the degree of inflammation than the leucocyte count (Beaty et al, 1968). These workers reported highly significant differences in C.S.F. L.D.H. activity between pneumococcal and meningococcal meningitis, and explained it on the basis of the difference in the degree of inflammation produced by the two. These observations were contrary to those reported by Feldman et al in 1975.

Evaluation of C.S.F. L.D.H. may help in diagnosis of culture negative acute bacterial meningitis (Hallock et al, 1978) and in diagnosing controversial cases of tuberculous meningitis with inconclusive C.S.F. findings. (Khanna et al, 1977).

Therefore in general, it can be said that C.S.F. L.D.H. and G.O.T. can be of real diagnostic significance in acute bacterial and aseptic meningitis.

(b) Prognostic significance :

Various workers have reported high C.S.F. G.O.T.

values (above 25 units) as indicators of bad prognosis and have reported them to be associated with complications in cases of septic meningitis. (Reddy et al. 1972; Dalsey. 1969;) Shirole and Nair. 1974, however, could not correlate C.S.F. G.O.T. levels with course and prognosis of disease.

C.S.F. L.D.H. levels serving as an index to success of therapy in acute bacterial meningitis have been reported by Wroblewski et al. (1958) and Feldman et al. (1975).

Significantly higher C.S.F. L.D.H. values have been reported by Beaty et al. (1968) in patients with neurological sequelae and also in fatal cases. A persistently high level of C.S.F. L.D.H. has also been shown to be of bad prognostic significance (Gupta et al. 1982).

In acute tuberculous meningitis, Aronson. (1960) and Khanna et al. (1977) have reported observations similar to Wroblewski et al and Feldman et al.

4. <u>TIME OF C.S.F. EXAMINATION AND PEAK ENZYME ACTIVITY</u> :

The time of C.S.F. examination received much importance by Mallick and Bassett. (1964) and Laha and Bhargava. (1964). The former workers reported that an elevated level of activity could return to normal, if the C.S.F. was examined at a time, remote from the incident producing the elevation. They further observed that the rise was significant only if cases were examined within 7 days of

onset of stroke. In acute thrombotic episodes with infarction, elevated enzyme activity depends upon the temporal relationship between the incident and the removal of C.S.F. (Davies Jones, 1970).

Lending and Slobody in 1961 found increased C.S.F. G.O.T. levels minutes after cessation of hypoxia. These workers hypothesized that hypoxia produced incompetence of blood brain barrier and resulted in release of enzyme from brain cells. Smith et al, (1960), Akashi, (1966) and Mass in 1977 reported raised C.S.F. G.O.T. within hours after brain injury.

Wroblewski, (1958), Wolintz et al, (1969) and Chaudhuri et al, (1976) reported maximum C.S.F. L.D.H. activity between 1 to 3 days, normalising by tenth day of cerebrovascular episode. Similar findings were reported by Klun (1974), Green et al, (1957) and Mathur et al, (1965) for G.O.T. in C.S.F.

Studying acute strokes, Brodell in 1959 reported peak C.S.F. G.O.T. levels within 2-4 days of onset of stroke. Lieberman et al, (1957) and Wakim and Fleisher, (1956) reported maximum G.O.T. levels in C.S.F. within 3.5 days of the stroke. In 1978, Si Kohli et al, reported a tendency of rising C.S.F. G.O.T. in cerebrovascular accidents till fifth day and declining thereafter. Jakoby and Jakoby (1958) noted that L.D.H. assay values were higher when C.S.F. was obtained several days after the onset of symptoms.

The serum and spinal fluid showed moderate increases in C.S.F. G.O.T. activity in the first ten days of cerebrovascular episode in human beings (Fleisher et al. 1957). Brodell, (1959), found that large cerebral infarcts which terminated fatally produced significant transaminase elevations in C.S.F., rising during the first ten days of illness. Laha and Bhargava, (1964) and Singh et al, (1972) also observed increased G.O.T. activity during the first ten days of illness.

Peak S.G.O.T. levels have been reported to occur on 2nd-3rd day by Lieberman, (1957) and Mathur et al, (1965). Peak S.L.D.H. levels have been reported on fifth day and they decline thereafter (Chaudhari et al, 1976).

5. C.S.F. ENZYME LEVELS IN RELATION TO OTHER BIOCHEMICAL PARAMETERS IN INFECTIONS OF THE NERVOUS SYSTEM :

Some workers have reported a relationship between C.S.F. G.O.T. levels and protein content of C.S.F. (Miyasaki et al, 1958; Srivastava et al, 1971 and Reddy et al, 1972). However Katzman et al, (1957) did not observe any similar relationship. Shirole and Nair (1974) observed a rise in C.S.F. G.O.T. associated with a rise in cellular content of C.S.F. In acute bacterial meningitis, Wroblewski et al, (1958) reported a semiquantitative relation of leucocyte count with C.S.F. L.D.H. unlike Benty et al (1958) and Neches and Platt, 1968) who found no such relationship. All of these workers have however not reported any correlation of C.S.F. L.D.H. with C.S.F. appearance.

glucose, pro[redacted]ein, chloride and serologic reaction.

In acu[redacted] tuberculous meningitis no such

correlations [redacted]ave been reported by Khanna et al.

(1977) and H[redacted]llock et al, 1978).

MATERIAL AND METHODS

MATERIAL AND METHODS

The case material consisted of all consecutive cases of acute cerebrovascular accidents (based on Chusid's criteria, 1972), meningitides and encephalitides (diagnosed on the basis of clinical examination and routine cerebrospinal fluid examination) and normal controls (cases with no neurological, cardiac, skeletal, muscular and renal diseases likely to affect the transaminase and lactic dehydrogenase levels) presenting in the emergency and/or medical wards of M.L.B. Medical College and Hospital, Jhansi. Informed consent to the investigation was taken in all cases.

Acute myocardial infarction, hepatic, renal and skeletal muscle diseases, head injury and the diseases which result in a documented rise in the level of GOT, and LDH were excluded from this study.

All the neurological cases under study were subjected to a thorough interrogation and clinical examination. All the cases as well as normal controls were investigated as below :

1. Urine examination for sugar, albumin and microscopic findings.
2. Blood routine examination (TLC, DLC, Hb and ESR).
3. Blood sugar (fasting and postprandial) measurement.
4. Blood urea measurement.

5. Blood V.D.R.L. test.

6. Serum cholesterol measurement.

7. E.C.G. (wherever indicated).

8. C.S.F. biochemical examination and V.D.R.L. test.

9. Serum and C.S.F., Lactic dehydrogenase and Glutamic transaminase estimation.

METHODOLOGY :

Immediately after hospitalisation cerebrospinal fluid samples were obtained. Following lumbar puncture, a blood sample was also collected, soon after, in each case. Cerebrospinal fluid was centrifuged and separated from any sediment. Serum was separated from the clot within an hour after the collection of blood sample. Serum and supernatant CSF were stored at 0°C until enzyme estimation was done, which was not more than 48 hours in any case. Traumatic spinal fluid specimens were discarded.

The CSF and serum GOT levels were estimated by the colorimetric method of Reitman and Frankel (1957), as outlined below

The CSF and serum LDH levels were estimated by the colorimetric method as described by Wootton.

The serum and CSF enzyme estimations were repeated as and when necessary to determine the variations in enzyme activity during period of follow up.

ESTIMATION OF G.O.T. :

Principle :

Transfer of an aminogroup from an amino acid to an alpha keto acid is an important step in the metabolism of amino acids. Two enzymes occur in human tissues which catalyse reactions of this type. These are glutamic oxaloacetic transaminase (GOT, Aspartate amino transferase) and glutamic pyruvic transaminase (GPT, Alanine amino transferase). G.O.T. is involved in the following transamination :

alpha ketoglutaric acid + Aspartic acid $\xrightarrow{GOT}$ glutamic acid + oxaloacetic acid.

The oxaloacetate formed in the reaction with G.O.T. decarboxylates spontaneously to pyruvate. This pyruvate reacts with 2,4-dinitrophenyle hydrazine which is measured in the colorimeter at 510 milli micron.

Method :

(Reitman and Frankel, 1957).

Reagents :

G.O.T. substrate - (200 mM-DL-aspartic acid; 2mM-alpha-ketoglutarate).

13.3 g of DL aspartic acid was dissolved in the minimum amount of N-sodium hydroxide which dissolved it and a solution was produced with a pH of 7.4. About 90 ml was required. 0.146 g of alpha ketoglutaric acid was

added and dissolved by adding a little more sodium hydroxide. The pH was adjusted to 7.4 and the solution was made to 500 ml with phosphate buffer. It was divided into 10 ml portions and stored frozen at -15°.

Stock pyruvate standard :

(20 mM) 220 mg of sodium, pyruvate was dissolved per 100 ml of phosphate buffer. It was stored at -15° in 1 ml aliquots.

Working pyruvate standard :

(4 mM). The stock standard was diluted 1 in 5 with phosphate buffer and stored at -15°. It was prepared fresh each week.

2,4-dinitrophenyl hydrazine :

(1 mM) 19.8 mg of dinitrophenyl hydrazine was dissolved in 10 ml of concentrated hydrocholoric acid and made to 100 ml with water. It was kept at room temperature in a brown bottle.

0.4 N-sodium hydroxide :

16 g of sodium hydroxide per litre in water.

Phosphate buffer :

(pH 7.4). 11.3 g of dry anhydrous disodium hydrogen phosphate and 2.7 g of dry anhydrous potassium dihydrogen phosphate per litre in water. The pH was checked and it was stored at 4°.

Test :

0.5 ml of substrate was warmed in a water bath at 37° for 3 min. 0.1 ml of serum/CSF was added, mixed and incubated for exactly 60 min. The tubes were removed from the bath, 0.5 ml of DNPH solution was added immediately and was mixed well.

Control :

0.5 ml of substrate was mixed with 0.5 ml of DNPH solution and 0.1 ml of serum/CSF was added.

Standard :

0.1 ml of working pyruvate standard was mixed with 0.4 ml of substrate, 0.1 ml of water and 0.5 ml of DNPH solution.

Blank :

0.5 ml of substrate, 0.1 ml of water and 0.5 ml of DNPH were mixed in a test tube.

The DNPH was allowed to react in all tubes for 20 min. at room temperature, then 5 ml of 0.4 N-sodium hydroxide was added, mixed well and left for a further 10 min.

The pyruvate formed by the serum/CSF was responsible for the difference between test and control (T-C). The pyruvate in 0.1 ml of working standard (0.4 micro mole) produced the difference between standard and Blank (S-B). So the pyruvate formed in 60 min. by 0.1 ml of serum/CSF was :

$$\frac{T-C}{S-B} \times 0.4 \text{ micro mole}$$

Thus the pyruvate formed per min. per litre of serum/CSF was :

$$= \frac{T-C}{S-B} \times 0.4 \times \frac{1}{60} \times \frac{1000}{0.1}$$

$$= \frac{T-C}{S-B} \times 67 \text{ micro mole}$$

The calculated pyruvate was converted into I.U. per litre by Wootton's reference table.

ESTIMATION OF L.D.H. :

Principle :

Lactic dehydrogenase is an enzyme of almost universal distribution in the body which catalyses the reversible transformation of pyruvate to lactate.

$$\text{Pyruvic Acid} + NADH + H^+ \xrightarrow{LDH} \text{Lactic Acid} + NAD^+$$

Pyruvate is reduced by incubation with serum or CSF in the presence of coenzyme $NADH_2$. The reaction is stopped by adding DNPH solution which reacts with the remaining pyruvate forming a hydrazone. The amount of unreacted pyruvate is found by measuring the brown colour, produced when the hydrazone is made alkline. The determination is performed at 25° because some of the serum/CSF is very sensitive to heat.

Method :

Reagents :

Buffer :

(pH 7.4) 11 g of anhydrous disodium hydrogen phosphate and 2.7 g of anhydrous potassium dihydrogen phosphate per litre in water.

Stock sodium pyruvate :

(37.5 mM) 415 mg of sodium pyruvate buffer. It was divided into 1 ml. samples and kept at -15°.

Working sodium pyruvate buffered substrate :

(0.75 mM). Stock pyruvate solution was dissolved 1in 50 with phosphate buffer. Fresh dilutions were made daily.

Reduced nicotinamide adenine dinucleotide- (NADH) :

10 mg $NADH_2$ per/ml of phosphate buffer. It was made fresh for each batch of tests.

2,4-dinitrophenylhydrazine :

(2 mM) 400 mg of dinitrophenylhydrazine was dissolved in 85 ml of concentrated hydrochloric acid. It was made up to 1 litre with water and stored in a dark bottle.

0.4 N sodium hydroxide :

16 g of sodium hydroxide per litre of water.

Method :

Test :

1 ml of buffered substrate was mixed with 0.1 ml of serum or CSF. The mixture was placed in a water bath at 25°. After a few minutes the reaction was started by

adding 0.1 ml of $NADH_2$ solution. It was incubated for exactly 15 min. the test tube was removed from the bath and 1 ml of DNPH solution was added immediately with mixing.

Control :

1 ml of substrate, 0.2 ml of buffer and 1 ml of DNPH solution.

Blank :

1.2 ml of buffer and 1 ml of DNPH solution. All the tubes were allowed to stand at room temperature for 20 min. 10 ml of 0.4 N sodium hydroxide solution was added to each and mixed. The coloured solutionswere compared at 510 milli micron after 10 min.

The control tube contained 0.75 micro mole of pyruvate.

Amount of reacted pyruvate was $\frac{C-T}{C-B}$ X 0.75 micro mole.

This was the effect of the enzyme in 0.1 ml of serum or CSF acting for 15 min. The pyruvate reacting per minute per litre of serum/CSF was thus :

$$\frac{C-T}{C-B} \times 0.75 \times \frac{1}{15} \times \frac{1000}{0.1}$$

$$LDH = \frac{C-T}{C-B} \times 500 \text{ (micro mole per min. per litre).}$$

OBSERVATIONS

O B S E R V A T I O N S

The present work was undertaken on patients of acute neurological episodes admitted to the medical and emergency wards of M.L.B. Medical College Hospital, Jhansi, during a period of 9 months viz. from June 1982 to February, 1983.

The study group consisted of 58 patients including 16 cases of cerebral infarction (27.6%), 12 each of intra-cranial haemorrhage and tuberculous meningitis (20.7%), 10 of Pyogenic meningitis (17.2%) and 8 with miscellaneous conditions (13.8%). The category of cerebral infarction consisted of 11 cases of (19%) cerebral thrombosis and 5 of cerebral embolism (8.6%). Out of 12 cases grouped as intracranial haemorrhage 7 (12.1%) were thought of cerebral haemorrhage and 5 (8.6%) of subarachnoid haemorrhage. The miscellaneous group consisted of 8 cases including 3 each (5.2%) of transient ischaemic attacks and encephalitis and 2 (3.4%) of cortical vein thrombosis (Table-I).

Twenty age and sex matched individuals were investigated to serve as controls. The mean age of the study group was 40.6±17.4 years while that of controls was 39.9±16.1 years, there being no significant difference between the two ($t = 0.16$, $d.f. = 76$, $P > 0.50$) (Table-II).

Thirty six cases out of 58(62.1%) in the study group were males and the remaining 22 (37.9%), females. In controls the number of males was 12 (60.0%) and that

TABLE - I

Distribution of cases of different neurological disorders included in the study group

Group	No.of cases	%
1. Infarction	16	27.6
Thrombosis	11	19.0
Embolism	5	8.6
2. Haemorrhage	12	20.7
Cerebral	7	12.1
Subarachnoid	5	8.6
3. Tuberculous meningitis	12	20.7
4. Pyogenic meningitis	10	17.2
5. Miscellaneous	8	13.8
Transient ischaemic attacks	3	5.2
Encephalitis	3	5.2
Cortical vein Thrombosis	2	3.4
Total	58	100.0

TABLE - II

Distribution of cases in study and control group by age

Age group (years)	Study group No.	%	Control group No.	%
10 - 19	7	12.0	2	10.0
20 - 29	11	19.0	4	20.0
30 - 39	9	15.5	4	20.0
40 - 49	11	19.0	4	20.0
50 - 59	9	15.5	3	15.0
60 and above	11	19.0	3	15.0
Total	58	100.0	20	100.0
Mean ± S.D.		40.6±17.4		39.9±16.0
Statistical significance	t = 0.16, d.f. = 76, P = 0.50			

of females 8 (40.0%). In this respect too, the two groups were comparable (X^2= 0.03, d.f. = 1, P > 0.05) (Table-XXI).

TABLE - XXI

Distribution of cases in the study and control groups by sex

Sex	Study group No.	%	Control group No.	%
Male	36	62.1	12	60.0
Female	22	37.9	8	40.0
Total	58	100.0	20	100.0
Statistical significance	X^2 = 0.03, d.f. = 1, P > 0.05			

The mean serum and cerebrospinal fluid (C.S.F.) glutamic oxaloacetic transaminase (G.O.T.) values in the control group were 9.85 ±4.6 I.U./L and 5.5±2.5 I.U./L respectively. Mean serum and C.S.F. lactic dehydrogenase (L.D.H.) values in this group were 94.25± 38.6 I.U./L and 16.2±4.9 I.U./L respectively (Table-IV).

TABLE - IV

Showing serum and C.S.F. values of G.O.T. and L.D.H. in controls

Enzyme		m ± S.D. (I.U./L)
G.O.T.	Serum (n=20)	9.85±4.6
	C.S.F. (n=20)	5.5±2.5
L.D.H.	Serum (n=20)	94.25±38.6
	C.S.F. (n=20)	16.2±4.9

The enzyme values in the different categories of the study group varied considerably, increasing in some, decreasing in some and remaining unchanged in some categories. It would not therefore be legitimate to pool them together as the rise and fall therein would cancel out each other. The various diagnostic groups are hence being analysed separately in comparison to the control group.

CEREBRAL INFARCTION :

There were 16 cases with cerebral infarction out of which 11 were of cerebral thrombosis and 5 of cerebral embolism. Out of these 16 cases presenting at the initial examination, only 13 could be followed up after third day (two patients left against medical advice and 1 expired). On the second follow up, only 7 of the original 16 could be studied (5 had been discharged on request due to improvement in clinical condition and 1 left against medical advice). Out of these 7 cases one expired and 6 improved. Mean serum and C.S.F. G.O.T. values, on admission, were significantly higher, compared to controls, being 13.0±4.5 I.U./L (P < 0.05) and 13.2±6.6 I.U./L (P < 0.001) respectively. On first follow up, the mean serum G.O.T. (15.2±3.7 I.U./L) showed a rising trend whereas the mean C.S.F. G.O.T. (11.2±6.1 I.U./L) registered a decline. Nevertheless, both these values were significantly higher, compared to controls (P < 0.005 and < 0.001 respectively). Even on the second follow up, the mean serum and C.S.F.

G.O.T. values continued to be significantly raised, being 15.2±2.7 I.U./l. (P < 0.01) and 10.0±6.6 I.U./l. (P < 0.02) respectively (Table VI). Thus serum G.O.T. was found to be raised in all cases with cerebral infarction with a peak value between fourth and seventh day, after which there was a decline. The values, however, had not come back to normal levels even on the eleventh day. C.S.F. G.O.T. On the other hand registered a peak within the first three days of the occurrence of the cerebrovascular episode. The values here too, had not come down to normal even on the eleventh day.

Out of 16 cases of cerebral infarction, only 2 expired. Three cases left the hospital against medical advice in a deteriorating condition. Out of 5 cases of cerebral embolism 4 had definite clinical source of the embolus. Highest value of C.S.F. G.O.T. (27 I.U./l.) was recorded in a case of cerebral thrombosis, who eventually expired. In cerebral thrombosis the maximum S.G.O.T. value was to the tune of 22 I.U./l., the patient here, however, improved.

Serum Lactic Dehydrogenase (S.L.D.H.) values were within normal limits in cases with cerebral infarction. C.S.F. levels of the enzyme were, however, significantly raised from the beginning with a mean peak of 46.6±12.5 I.U./l. at the initial examination (P < 0.001). The value declined to 38.9±12.3 I.U./l. (P < 0.001) on the first follow up, and to 36.6±11.3 I.U./l. (P < 0.001) on the

second follow up (Table-VI). Maximum C.S.F. S.D.H. was 70 I.U./L. in a case who subsequently expired.

When cases with cerebral thrombosis and embolism were compared, no significant difference in peak C.S.F. G.O.T. and L.D.H. values could be found ($P > 0.1$). However there was a significant difference between S.G.O.T. values, those in cerebral embolism being higher ($P < 0.05$). On comparing cerebral haemorrhage to subarachnoid haemorrhage highly significant differences in C.S.F. and S.G.O.T. values were found, those in cerebral haemorrhage being higher ($P < 0.001$). However no significant alteration in C.S.F. L.D.H. values could be found ($P > 0.01$).

TABLE - V

G.O.T. and L.D.H. values (m ± S.D.) in serum and C.S.F. for cases with infarction and controls

Enzymes (I.U./L)	Cases with infarction: On admission (n=16)	I Followup (n=11)	II Followup (n=7)	Controls (n=20)
Serum :				
G.O.T.	13.0±4.5	13.2±3.7	15.2±2.7	9.8±4.6
L.D.H.	95.8±21.5	94.2±21.0	90.0±18.5	94.2±38.6
C.S.F. :				
G.O.T.	15.8±6.6	11.3±6.1	10.0±6.6	5.5±2.5
L.D.H.	46.6±12.5	32.6±12.2	26.6±11.3	16.2±4.9

TABLE - VI

Statistical significance of the difference of the enzyme values between cases with infarction and controls

Enzyme	Significance of the difference: On admission (n=16) t	D.F.	P	I Followup (n=13) t	D.F.	P	II Followup (n=7) t	D.F.	P
SERUM :									
G.O.T.	2.1	34	<0.05	3.3	31	<0.005	2.9	25	<0.01
L.D.H.	0.04	34	>0.01		—		0.3	25	>0.10
C.S.F. :									
G.O.T.	5.3	34	<0.001	3.9	31	<0.001	2.6	25	<0.02
L.D.H.	8.4	34	<0.001	7.4	31	<0.001	6.9	25	<0.001

HAEMORRHAGE :

This group consisted of 12 cases including 7 of cerebral haemorrhage and 5 of subarachnoid haemorrhage. Out of these 12 cases only 5 could be followed up on fourth to seventh day (5 cases with cerebral haemorrhage and 1 with subarachnoid haemorrhage expired within the first 72 hours and 1 case of the latter was discharged on request due to clinical improvement). Out of these 5 cases studied during fourth to seventh day, one with subarachnoid haemorrhage was discharged on improvement and the other two cases with cerebral haemorrhage either expired or left the hospital against medical advice. The remaining two cases with subarachnoid haemorrhage were also studied for the third time viz. on eight to eleventh day. However, due to small number of cases, no statistical analysis was carried out.

Serum G.O.T. was raised to peak activity at the beginning of episode itself unlike that in infarction where peak value was found between fourth and seventh day. Mean S.G.O.T. values were 37.2±17.0 I.U./L. and 27.0±18.2 I.U./L. on two examinations (Table-VII). both were markedly higher compared to controls, the differences being highly significant (P < 0.001 in both cases) (Table-VIII). C.S.F. G.O.T. was raised on both the occasions (admission and first followup) with the peak in the first 72 hours. Thus the trend was similar to that observed in infarction. The mean C.S.F. G.O.T. values were 34.9±13.6 I.U./L. and 29.4±13.4 I.U./L. respectively (Table-VII) both being significantly higher compared to controls (P < 0.001) (Table-VIII). Serum L.D.H. was within normal limits in these cases. C.S.F. L.D.H. however showed remarkable elevations with peak values of 225.3±48.7 I.U./L. on first examination which declined to 167.6±14.4 I.U./L. on second examination (Table-VII). both the values were significantly higher as compared to controls (P < 0.001) (Table-VIII). On second followup, which consisted of only two cases with subarachnoid haemorrhage, the S.G.O.T. and C.S.F. G.O.T. values were 16 I.U./L. 20 I.U./L. and 14 I.U./L. 15 I.U./L. respectively. C.S.F. L.D.H. was found to be 110 I.U./L. and 96 I.U./L. in these two cases.

Overall, the mean output values of S.G.O.T. and C.S.F. G.O.T. were 21.4±6.2 I.U./L. and 21.8±2.9 I.U./L.

in subarachnoid haemorrhage as compared to higher S.G.O.T. and C.S.F. G.O.T. values (48.4±12.1 I.U./L; 44.3±9.2 I.U./L) in cases with cerebral haemorrhage. Mean C.S.F. L.D.H. in subarachnoid haemorrhage was 204±3.2 I.U./L as compared to 240.4±54.9 I.U./L in cerebral haemorrhage.

TABLE - VII

G.O.T. and L.D.H. values (m ± S.D.) in serum and C.S.F. for cases with haemorrhage and controls

Enzymes (I.U./L)	Cases with haemorrhage On admission (n=12)	Cases with haemorrhage 1 followup (n=5)	Controls (n=20)
Serum :			
G.O.T.	37.2±17.0	27.8±12.2	9.8±4.6
L.D.H.	97.3±16.4	90.8±19.3	94.2±20.6
C.S.F. :			
G.O.T.	34.9±13.6	29.4±13.4	5.5±2.8
L.D.H.	225.3±48.7	167.6±14.6	16.2±4.9

TABLE - VIII

Statistical significance of the difference of enzyme values between cases with haemorrhage and controls

Enzyme	Significance of the difference: On admission t	d.f.	P	1 followup* t	d.f.	P
Serum :						
G.O.T.	6.9	30	< 0.001	4.2	23	< 0.001
L.D.H.	0.3	30	> 0.05	0.2	23	> 0.05
C.S.F. :						
G.O.T.	9.5	30	< 0.001	7.9	23	< 0.001
L.D.H.	19.3	30	< 0.001	40.5	23	< 0.001

*7 out of the initial 12 cases had expired by the time of 1 followup.

Out of 12 cases, 7 expired (1 with subarachnoid haemorrhage and 6 with cerebral haemorrhage). Six of

these 7 cases expired within 72 hours of admission. The remaining one patient expired on the sixth day.

TUBERCULOUS MENINGITIS :

There were 12 cases (20.7%) with tuberculous meningitis. All of them had history of less than 7 days duration and all were examined for C.S.F. and serum enzyme values at weekly intervals.

TABLE - IX

G.O.T. and L.D.H. values (m ± S.D.) in serum and C.S.F. for cases with tuberculous meningitis and controls

Enzyme (I.U./L)	Cases with tuberculous meningitis		Controls
	On admission (n=12)	Followup (n=9)	(n=20)
Serum :			
G.O.T.	10.0±2.6	9.11±2.4	9.2±4.6
L.D.H.	93.9±26.5	87.3±22.3	94.2±38.6
C.S.F. :			
G.O.T.	12.5±3.4	10.6±3.2	3.5±2.5
L.D.H.	91.0±41.3	70.3±42.8	16.2±4.9

Out of 12 cases, 9 could be followed up a week later (one got discharged on request and 2 expired). On second followup only a single patient was available as 2 had expired and 7 had got discharged, on request due to clinical improvement.

C.S.F. G.O.T. values were significantly elevated (Table-X) as compared to controls, on admission.

These values were also the highest (12.5±3.4 I.U./L) (Table-IX). There was a decline to a mean of 10.6±3.2 I.U./L on first followup. Eleven out of 12 patients (91%) had

initial C.S.F. G.O.T. values up to 15 I.U./L. Out of these 11, 3 patients expired during the study (2 in the first week and 1 in the second week). The remaining twelfth patient had a C.S.F. G.O.T. value of 22 I.U./L on admission. He expired in the second week. Out of the 9 patients who improved, 3 (33%) showed sequelae in the form of lateral rectus palsy, optic atrophy and right sided hemiparesis and their initial C.S.F. G.O.T. values were in the range of 11-12 I.U./L. S.G.O.T. estimations done simultaneously did not show any significant change from the controls ($P > 0.05$) (Table-X). Cerebrospinal fluid L.D.H. values were markedly elevated on admission as well as on first follow up (mean 91± 41.3 I.U./L and 70.2±43.8 I.U./L respectively) (Table-IX). These values were highly significant on comparison to controls ($P < 0.001$ in each case) (Table-X). Out of the 12 cases only 3 (25%) had

TABLE - X

Statistical significance of the difference of enzyme values between cases with tuberculous meningitis and controls

Enzyme	Significance of the difference on admission (n=12)			Significance of the difference on follow up (n=9)		
	t	d.f.	P	t	d.f.	P
Serum :						
G.O.T.	0.1	30	> 0.05	0.4	27	> 0.05
L.D.H.	0.02	30	> 0.05	0.5	27	> 0.05
C.S.F.						
G.O.T.	4.7	30	< 0.001	4.6	27	< 0.001
L.D.H.	8.1	30	< 0.001	5.6	27	< 0.001

initial C.S.F. L.D.H. values below 60 I.U./L of which none

expired. Six patients (30%) had values ranging between 60 to 120 I.U./l. and of these 2 expired. Three patients had values beyond 120 I.U./l. and 2 of them expired and, one improved. Thus, out of 4 patients who expired, 2 had values between 60-220 I.U./l. and 2 had values beyond 120 I.U./l.. The 3 patients who improved with sequelae had initial C.S.F. L.D.H. in the range of 57-84 I.U./l.. No statistically significant alterations were seen in serum L.D.H. ($P > 0.05$) (Tables- XX and X).

PYOGENIC MENINGITIS :

Ten patients out of 58 (17.2%) had pyogenic meningitis. All of them had a history of less than 7 days duration and all were examined for C.S.F. and serum values at weekly intervals. Out of 10 cases, only 4 could be followed up a week later (4 of them expired, 1 left against medical advice and one had to be discharged on request). Of these 4 cases examined on first follow up, 2 left against medical advice and 2 improved and had to be discharged. None of them could be reviewed up after 2 weeks. C.S.F. G.O.T. showed peak levels on admission (mean 27.2±3.6 I.U./l.) whereafter the levels declined to 22.2± 2.6 I.U./l. on the first follow up; (Table-XI) both values being highly significant when compared to controls ($P < 0.001$) (Table-XII). Eight out of 10 patients (80%) had C.S.F. G.O.T. values between 15-30 I.U./l.. Out of these 2 expired, 3 left the hospital against medical advice and 3 improved. Two cases (20%) had C.S.F. G.O.T. levels

beyond 30 I.U./L and both of them expired. S.G.O.T. values, did not show significant alterations in pyogenic meningitis (P > 0.05) (Table-XII) C.S.F. L.D.H. values

TABLE - XI

G.O.T. and L.D.H. values (m ± S.D.) in serum and C.S.F. for cases with pyogenic meningitis and controls

Enzyme (I.U./L)	Cases with pyogenic meningitis		Controls
	On admission (n=10)	Follow-up (n=4)	(n=20)
Serum :			
G.O.T.	9.9±2.1	8.2±1.7	9.8±3.6
L.D.H.	86.1±16.9	79.3±19.9	94.2±3.6
C.S.F. :			
G.O.T.	27.2±3.6	22.2±2.6	5.5±2.5
L.D.H.	160.6±52.9	92.3±32.8	16.2±4.9

TABLE - XII

Statistical significance of the difference of enzyme values between cases with pyogenic meningitis and controls

Enzyme	Significance of the difference on admission (n=10)			Follow up (n=4)		
	t	d.f.	P	t	d.f.	P
Serum :						
G.O.T.	0.03	28	> 0.05	0.7	22	> 0.05
L.D.H.	0.6	28	> 0.05	0.7	22	> 0.05
C.S.F. :						
G.O.T.	19.2	28	< 0.001	13.9	22	< 0.001
L.D.H.	13.0	28	< 0.001	6.9	22	< 0.001

were significantly raised (P < 0.001 in each case) (Table-XII) from the time of initial examination (160.6± 52.9 I.U./L) to first follow up (92.3±32.8 I.U./L) (Table-XI). Out of the 10 cases 4 (40%) had initial C.S.F.

L.D.H. values between 100-150 I.U./L. Three of them improved and one left against medical advice. Three cases (30%) had values between 150-200 I.U./L. two of them expired and one left against medical advice. The remaining three cases (30%) had C.S.F. L.D.H. values beyond 200 I.U./L. of these two expired and 1 left against medical advice. Thus out of 4 cases who expired 2 had C.S.F. L.D.H. values between 150-200 I.U./L. and the remaining two had values beyond 200 I.U./L.

No statistically significant alterations were seen in serum L.D.H. in pyogenic meningitis ($P > 0.05$) (Table-XXI).

MISCELLANEOUS GROUP :

This group consisted of 3 cases each (5.2%) of transient ischaemic attacks and encephalitis, and 2 cases of cortical vein thrombosis (3.4%). All cases with transient ischaemic attacks had normal serum and C.S.F. G.O.T. and L.D.H. values. Both the cases with cortical vein thrombosis had elevated C.S.F. G.O.T. levels (21± 2.8 I.U./L), which when compared to controls were highly significant ($P < 0.001$). S.G.O.T. values were within normal limits in these cases. Both the cases had statistically significant selvation in C.S.F. L.D.H. values (mean 37±1.4 I.U/L.) ($P < 0.001$) in contrast to serum L.D.H. which was normal. Both recovered.

In the three cases with encephalitis, one expired after the first followup, one left against medical advice

and one improved. However, enzyme levels of C.S.F./Serum-G.O.T./L.D.H. were within normal limits in these cases.

RELATION OF ENZYME LEVELS WITH PROGNOSIS (ULTIMATE CLINICAL OUTCOME) :

When peak C.S.F. enzyme levels were compared between improved and expired cases of various diagnostic groups, it was found that the former had a definite bearing upon the prognosis (Table-XIII). The mean C.S.F. G.O.T. between improved and expired cases of cerebral infarction showed a highly significant difference (P < 0.001) (Table-XIII). The 2 expired cases had a mean C.S.F. G.O.T. of 25.5±2.2 I.U./L whereas the 11 improved cases had a value of 12.0±4.7 I.U./L (Table-XIII). Mean C.S.F. L.D.H. values were 41.5±10.8 I.U./L in improved cases and 66±5.7 in expired cases (Table-XIII). This difference too was statistically significant (P < 0.01) (Table-XIII).

In cases with haemorrhage, all the improved cases had subarachnoid haemorrhage. Out of 7 cases, who expired, 6 had cerebral and 1 had subarachnoid haemorrhage. The enzymes (C.S.F. G.O.T. and L.D.H.) showed significant difference (P < 0.001 and < 0.01 respectively) between improved and expired cases. Mean C.S.F. G.O.T. levels in the two groups were 20.8±2.8 I.U./L and 42.6±11.3 I.U./L respectively (Table-XIII). Mean C.S.F. L.D.H. levels were 204±37.21 I.U./L and 244.5±30.2 I.U./L respectively (Table-XIII). In cases with tuberculous meningitis 8 cases

improved and 4 expired. Out of 8 cases who improved, 3 improved with sequelae. However the mean enzyme levels in these cases did not differ significantly from the rest of theimproved ones ($P > 0.5$). Mean C.S.F. G.O.T. and L.D.H. levels in the improved cases were 11.1±1.7 I.U./L and 76.4±37.4 I.U./L respectively whereas in the expired cases the values were 15.3±4.6 I.U./L and 120.3±35.9 I.U./L respectively (Table-XIII). The difference with respect to C.S.F. G.O.T. values was found to be statistically significant ($P < 0.05$) (Table-XIII). Whereas the corresponding differences in L.D.H. values were not statistically significant ($P > 0.05$) (Table-XIII).

When the mean C.S.F. G.O.T. and L.D.H. levels between improved and expired cases with pyogenic meningitis were compared, highly significant differences emerged. The improved cases had mean C.S.F. G.O.T. and L.D.H. values of 22.7±2.1 I.U./L and 116.6±13.8 I.U./L respectively, whereas the expired ones had a value of 30±1.8 I.U./L and 212.8±18. I.U./L respectively ($P < 0.005$ and < 0.001 respectively) (Table-XIII). On comparing serum enzyme variations between improved and expired cases in various groups it was found that in haemorrhage cases the S.G.O.T. had statistically significant difference between the improved (19.2±4.6 I.U./L) and expired (47.6±13.3 I.U./L) cases ($P < 0.005$) (Table-XIV). No difference in serum enzymes, however, could be found between other diagnostic groups among the improved and expired cases.

TABLE - XXII

Peak C.S.F. enzyme values† (m ± S.D.) in relation to prognosis in different diagnostic groups.

Disease Group	G.O.T. Improved No.	m ± S.D.	Expired No.	m ± S.D.	L.D.H. Improved No.	m ± S.D.	Expired No.	m ± S.D.
Infarction (16)	11	12.0±4.7*	2	25.5±2.2*	11	41.5±10.8	2	66±5.7*
Haemorrhage(12)	4	20.8±2.8*	7	42.6±11.3*	4	204±37.2*	7	244.5±50.2*
Tuberculous meningitis (12)	8	11.1±1.7*	4	15.3±4.8*	8	76.4±37.4	4	120.3±35.9
Pyogenic meningitis (10)	3	22.7±2.1**	4	30.0±2.8*	3	116.4±13.8**	4	212.8±18.4**

† Mean peak enzyme values were compared between two groups - improved and expired.
* Differences significant at 5% level.
** Differences significant at 1% level.

TABLE - XIV

Peak serum enzyme values[?] (m ± S.D.) in relation to prognosis in different diagnostic groups

Disease group	G.O.T.				L.D.H.			
	Improved		Expired		Improved		Expired	
	No.	m ± S.D.	No.	M ± S.D.	No.	m ± S.D.	No.	m ± S.D.
Infarction (16)	11	15.0±4.0	2	14.5±3.5	11	95.0±17.6	2	73.0±18.4
Haemorrhage(12)	4	19.3±4.6*	7	47.6±13.3*	4	100.0±24.0	7	96.3±14.0
Tuberculous(8) meningitis (12)	8	10.9±2.0	4	8.3±3.0	8	85.0±25.0	4	111.7±21.7
Pyogenic meningitis (10)	3	10.3±3.0	4	10.3±2.0	3	86.7±25.0	4	85.5±14.5

? Mean enzyme levels were compared between two groups improved and expired.

* Differences significant at 1% level.

TABLE - XV

Correlation coefficients between C.S.F. enzymes and routine C.S.F. values (cells and proteins) in tuberculous meningitis*

C.S.F. routine values	Enzyme values	
	G.O.T.	L.D.H.
Cells	- 0.05	- 0.176
Proteins	+ 0.460	- 0.35

* None of the values was significant ($P > 0.05$).

TABLE - XVI

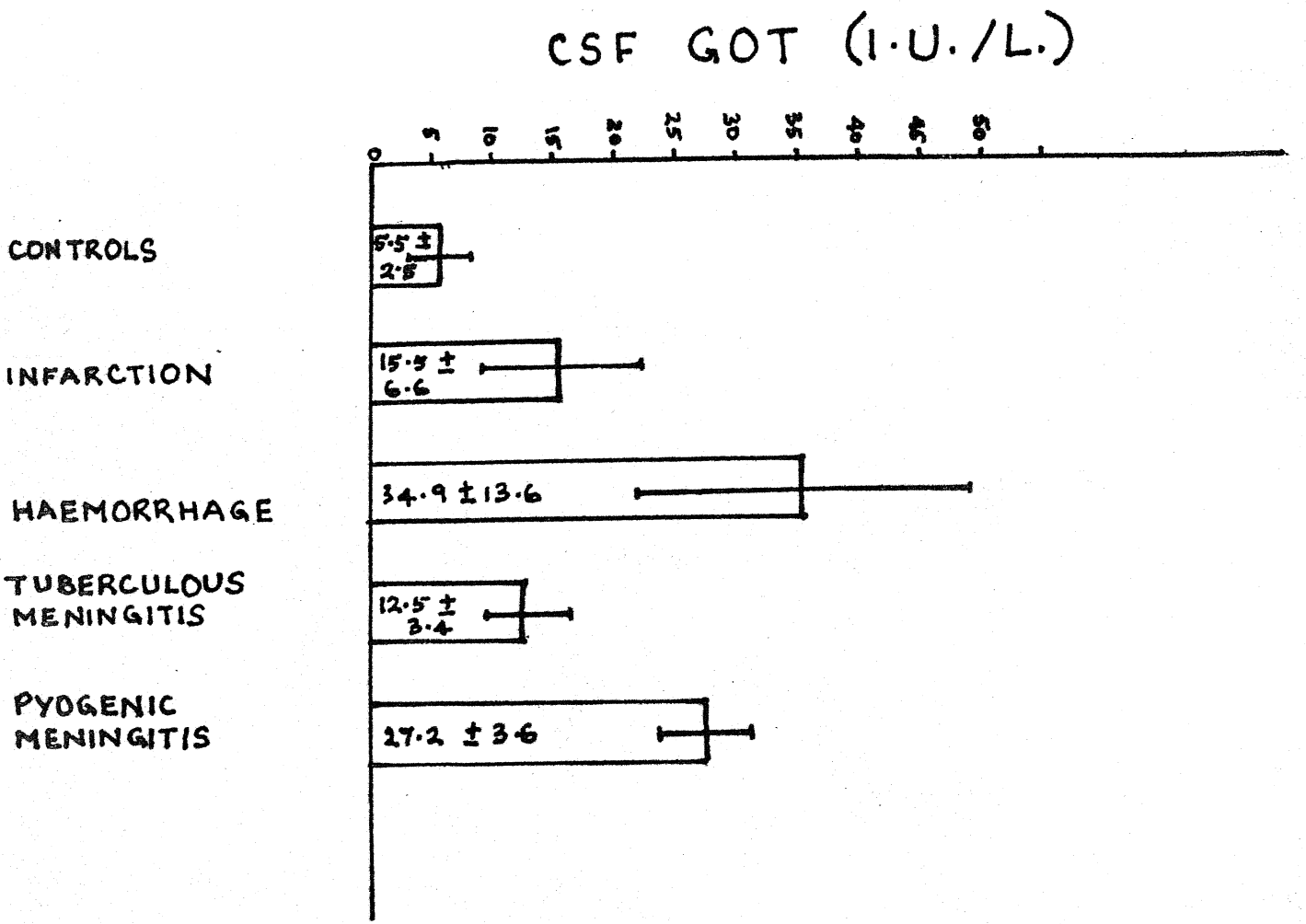
Correlation coefficients between C.S.F. enzymes and routine C.S.F. values (cells and proteins) in pyogenic meningitis*

C.S.F. routine values	Enzyme values	
	G.O.T.	L.D.H.
Cells	+ 0.04	- 0.02
Proteins	+ 0.38	+ 0.39

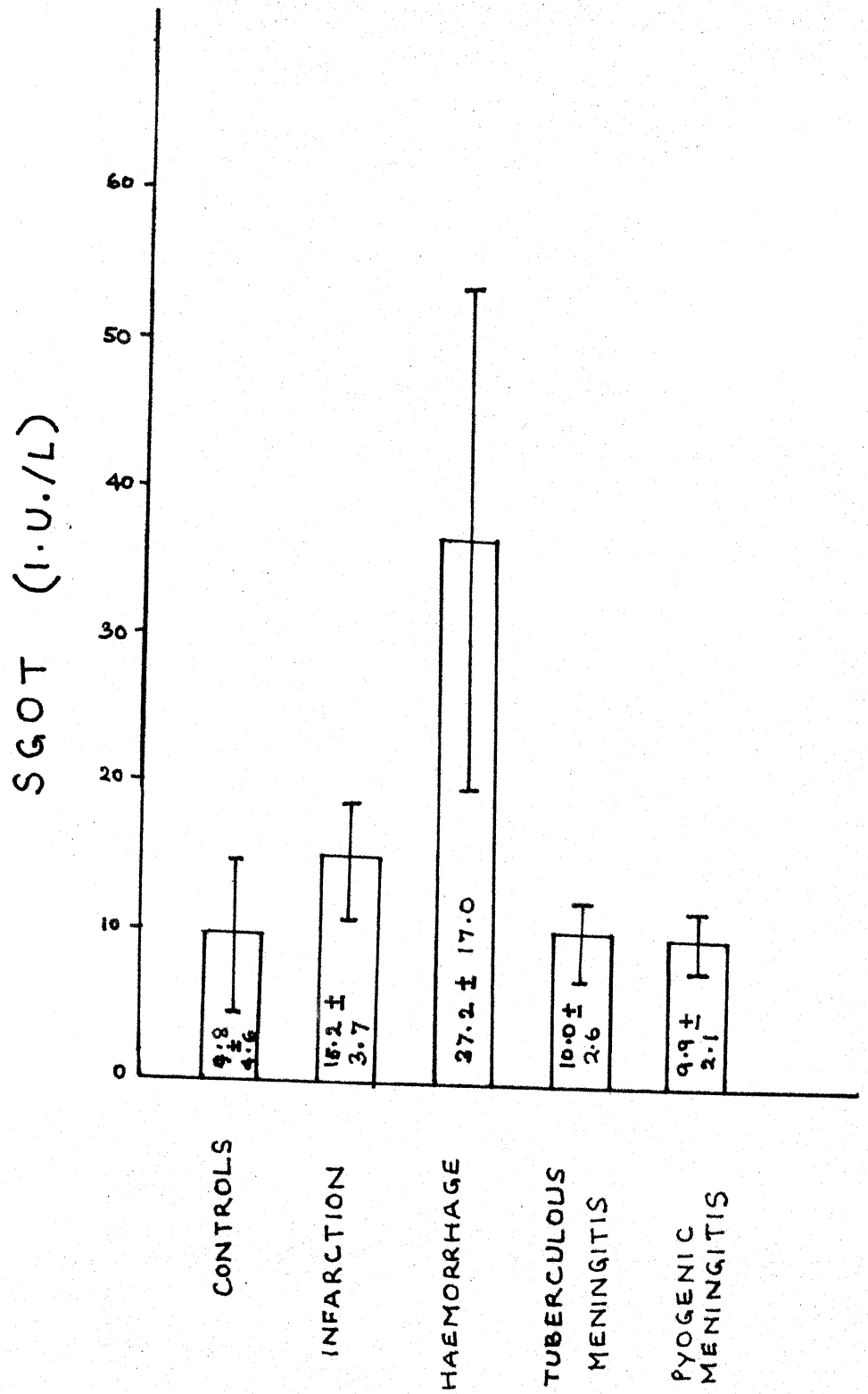
* None of the values was significant ($P > 0.05$)

There was no significant correlation between the C.S.F. enzyme levels and the routine C.S.F. values (cells and proteins) in tuberculous or pyogenic meningitis cases ($P > 0.05$) (Table-XV and XVI).

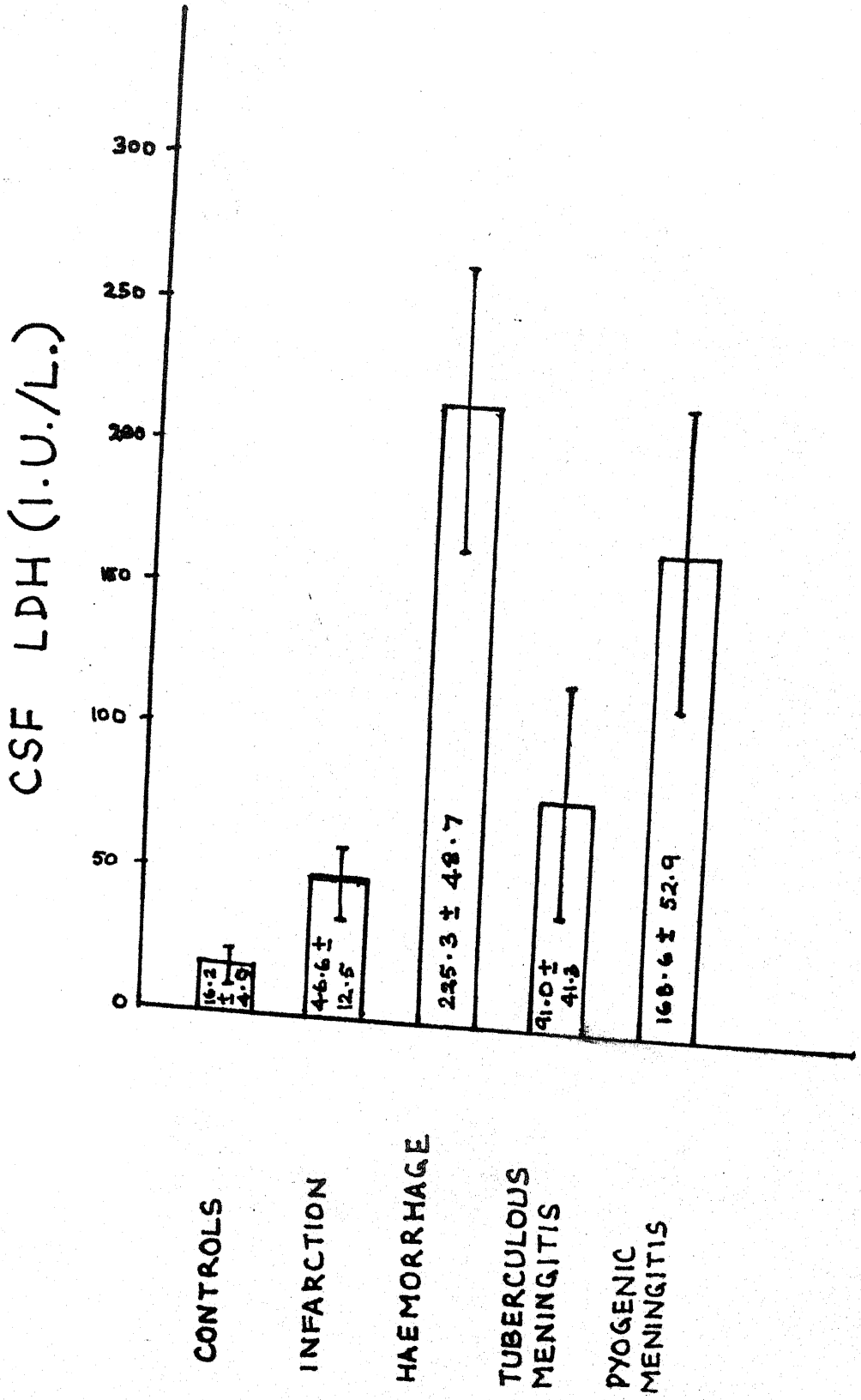
PEAK CSF-GOT VALUES IN DIFFERENT DIAGNOSTIC GROUPS



PEAK SGOT VALUES IN DIFFERENT DIAGNOSTIC GROUPS

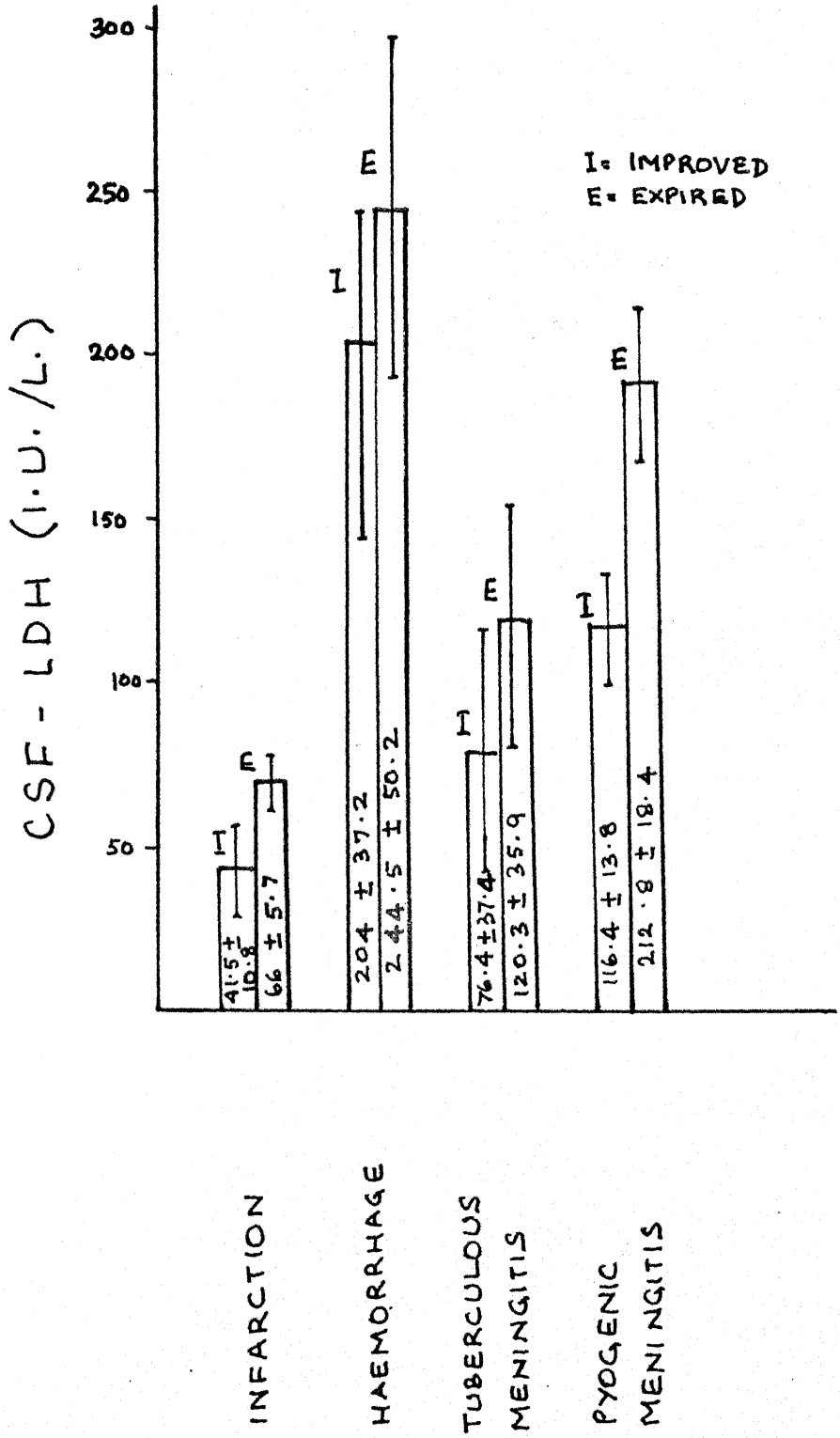


PEAK CSF-LDH VALUES IN DIFFERENT DIAGNOSTIC GROUPS



PEAK CSF-GOT VALUES IN IMPROVED AND EXPIRED CASES

PEAK CSF-LDH VALUES IN IMPROVED AND EXPIRED CASES



DISCUSSION

DISCUSSION

The use of enzymes as a diagnostic tool is not new. It was Karmen in 1955 who observed the serum glutamic oxaloacetic transaminase elevations in transmural myocardial infarction in man. The role of serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase in diseases of liver is another such example.

These changes are based on the fact that serum levels of enzymes rise whenever tissues abundant in them are damaged. That this property holds true for other body fluids also, has been a subject of much theoretical and practical attention. Long before this, Kaplan et al. (1938) had already focussed their minds on the enzymatic activities of the spinal fluid. Armed with the knowledge that damage to nervous tissue could cause elevations of enzyme levels in the spinal fluid, these workers studied various enzymes in normal and pathological spinal fluids. As time progressed interests changed from one disease to another. Interest in cerebrospinal fluid enzymology was heightened by Buchar (1952) who found increased triosephosphate isomerase activity in cerebrospinal fluid in cerebrovascular accidents. The recognition of the fact that intracellular enzymes could be absent from blood stream after central nervous tissue injury was presumed to reflect the influence of a blood brain barrier (Wiesisher et al. 1957).

The normal range of glutamic oxaloacetic transaminase and lactic dehydrogenase activity of cerebrospinal fluid obtained from persons without disease of the central nervous system has differed in various reports. These differences contribute to divergent interpretations of the changes of enzyme activity observed in pathologic states of the central nervous system (Wroblewski, 1958). Reports on the clinical significance of alterations in cerebrospinal fluid G.O.T. and L.D.H. activities also differ. Increases in these enzymes in C.S.F. are usually correlated with acute and significant injury to the central nervous system of diverse causes including those of thromboembolic, infections, degenerative and neoplastic origin. The increase in enzyme activity appears to occur at varying times after the onset of central nervous tissue injury. However, clinically significant central nervous tissue injury may occur without increased G.O.T. and L.D.H. activity. Correlation between serum and C.S.F. enzyme activities is yet to be firmly established. From the data presently available it would appear that a clear cut picture of role of C.S.F. enzymes in common neurological illnesses is yet to emerge.

In view of the present situation in this field, this study was planned to evaluate the importance of C.S.F. and serum levels of G.O.T. and L.D.H. in acute cerebrovascular episodes and encephalomeningitides. Stress was maintained on selecting only those cases who presented

within a certain specified time period after the onset of illness. This was done with a view to obviate the changes of a decline of enzyme activity after the destructive process induced rise in the enzyme levels. Diseases which could result in a documented rise in the enzymes being studied were excluded from the study group. Twenty patients with no disease likely to affect the levels of G.O.T. and L.D.H. served as controls.

SERUM GLUTAMIC OXALOACETIC TRANSMINASE AND LACTIC DEHYDROGENASE CHANGES IN CASES OF CEREBRAL INFARCTION AND INTRACRANIAL HAEMORRHAGE :

(a) Glutamic oxaloacetic transaminase :

This enzyme was significantly raised in all cases of cerebrovascular accidents. Serum G.O.T. increments in cerebrovascular accidents have also been reported by Lieberman et al (1957), Fleisher et al. (1957), Myerson et al. (1957), Brodell et al. (1959), Mathur et al. (1965) and Singh et al. (1972). However the above findings are at variance with those of Siekert and Fleisher (1956), Green et al. (1957) and Laha and Bhargava (1964). These workers did not report any serum G.O.T. increment in cerebrovascular accidents. Laha and Bhargava attributed this to the presence of an intact blood brain barrier.

Peak serum G.O.T. levels were obtained between fourth and seventh day of the onset of illness. However, in cases of haemorrhage the enzyme levels showed maximum rise in first three days and declined thereafter. In both

groups however, the levels did not touch normal till the last follow up which was up to eleventh day in infarction and up to seventh day in haemorrhage. Lieberman et al. (1957) reported peak levels of serum G.O.T. between one to five days of onset of illness. In another series of 21 patients of recent cerebrovascular accidents, Lieberman et al. in the same year reported maximal serum G.O.T. elevations from second day to third day after onset of symptoms in majority of their patients. Brodell et al. (1959) recorded maximum activity between second to fourth day of illness. Mathur et al (1965) reported peaks between second to fourth day of illness. However Singh et al (1972) reported peak serum G.O.T. values within first five days of illness except in cerebral thrombosis where it was observed between sixth to tenth day of illness. Kaul et al. (1978) reported rising serum G.O.T. values in their cases of cerebral thrombosis with peak in second week of onset of illness. The diversity in the observations of various workers, regarding the time of peak enzyme activity can in part be explained by the fact that the time of examination of blood carries much importance. An elevated level of activity may return to normal if the estimation is done at a time remote from the time of attack.

The early peak observed in cases of cerebral haemorrhage is in consonance with the findings of Mathur et al. (1965) who also observed an early peak in cases of

haemorrhage in comparison to thrombosis or embolism. These observations however are at variance with those of Singh et al. (1972) and Kaul et al. (1978) who did not report early peak values in cases of haemorrhage as compared to cerebral thrombosis or embolism. An earlier peak in cases of haemorrhage may be due to the presence of blood in C.S.F., thereby contributing to the rise in enzyme level induced by parenchymal damage. In the present work the serum G.O.T. levels failed to touch the normal levels even on last follow up (which was between eighth to eleventh day in infarction cases and between fourth to seventh day in cases of haemorrhage) and were statistically significant in both groups ($P < 0.01$ and < 0.001 respectively). Similar findings have been reported by Singh et al. (1972) and Kaul et al (1978). However Mathur et al (1965) could record near normal values of serum G.O.T. by twelfth day in cases of cerebral thrombosis and eighth day in cases of cerebral embolism.

Serum G.O.T. levels in cerebral haemorrhage were found to be significantly higher in comparison to cases of cerebral infarction in the present work. This could be due to admixture of blood with C.S.F. However, no definite diagnostic cut off level could be found for serum G.O.T. in our series.

Similar have been the observations of Singh et al. (1972) and Kaul et al (1978). Liebermann et al in 1957, however reported almost similar increments in serum G.O.T.

in cases with cerebral thrombosis and haemorrhage. Mathur et al. (1965) reported maximum serum G.O.T. elevation in cases of subarachnoid haemorrhage. Observation of rise in both C.S.F. and serum G.O.T. levels in the patients with cerebral infarction and haemorrhage may be due to disruption of blood brain barrier in acute cerebrovascular accidents. Mellick and Bassett (1964) have suggested that cerebral hypoxia leading to damage to the capillaries with subsequent leak may be an important factor.

(b) Lactic Dehydrogenase :

In the present study serum L.D.H. remained within normal limits. This observation is in conformity with that of Haieh and Blumenthal (1956), Fleisher et al. (1957), Wolinty et al. (1969) and Bedi et al. (1974). However, the above findings are at variance with those of Lowenthal (1961) and Chaudhri et al. (1976). These workers reported increments in serum L.D.H. activity in cases of cerebrovascular accidents. Chaudhari et al. (1976) reported maximum levels in cerebral haemorrhage. All of their serum enzyme increments came back to normal by tenth day after registering a peak on fifth day. No definite plausible explanation for this lack of rise in serum L.D.H. seems possible. The impermeability of blood brain barrier to L.D.H., the molecular structure and weight of this enzyme and the extent of cerebral damage responsible for raised cerebrospinal fluid L.D.H. activity may interplay with each other to produce a final effect.

CEREBROSPINAL FLUID GLUTAMIC OXALOACETIC TRANSAMINASE AND LACTIC DEHYDROGENASE LEVELS IN CASES WITH CEREBRAL INFARCTION AND HAEMORRHAGE :

(a) Glutamic oxaloacetic transaminase :

Significant elevations of cerebrospinal fluid G.O.T. levels were observed in cases with cerebral infarction and haemorrhage. The levels were found to be raised from the time of admission and maintained this trend till the last follow up which was between eighth to eleventh day in cases of infarction and fourth to seventh day in cases of haemorrhage. The peak values (15.5±6.6 I.U./L and 34.9±13.6 I.U./L respectively) in infarction and haemorrhage were obtained on admission itself and the levels showed a decline thereafter. When cerebral infarction was compared to haemorrhage significant difference in the enzyme levels of the two was found, the values in haemorrhage being decidedly higher ($P < 0.001$). In consonance with this finding Fleischer et al (1957) have reported moderate elevations of transaminase activity in a study of cerebrovascular disease in human beings. Lieberman et al (1957) found definite C.S.F. transaminase elevations in 7 out of their 15 patients with cerebral infarction. Raised cerebrospinal fluid G.O.T. values in cerebrovascular disease has been reported by Green et al (1957, 58), Brodall et al (1959), Mallick and Bassett (1964), Mathur et al (1965), Pradhan and Saxena (1965), Rama Rao.S. (1965), Singh et al (1972) Kohli et al (1978, 81) and Kaul et al (1978). However

Katzman (1957) and Myerson et al. (1957) did not find significant transaminase rise in C.S.F. in cases of cerebrovascular accidents.

Various workers have reported peak levels at different time intervals after the onset of stroke, in contrast to the peak reported within one to three days in the present study. Brodell et al (1959) reported peak values within two to four days of the onset of illness with large infarcts only. Significant elevations could only be found within a week after onset in cerebrospinal G.O.T. in the series reported by Mellick and Bassett (1964). In the series by Mathur et al. (1965), cerebrospinal fluid G.O.T. was elevated within 24 hours and reached its peak by second day. Pradhan and Saxena (1966) contended that significant rise of cerebrospinal fluid G.O.T. occurred in the C.S.F. samples collected before 16 hours after the onset of infarction. Singh et al. (1972) found peak activity within first five days. Peak activity on fifth day was also reported by Kohli et al. (1978). Kaul et al (1978) reported peak levels within a week in cases of haemorrhage and in second week in cases of cerebral infarction.

The diversity in enzyme values may be ascribed to the difference in clinical material. Slow extension of a thrombus over a period of some days may produce highest levels later on.

In the present series the enzyme levels did not touch normal till the last follow up which was between eighth to eleventh day in cases of infarction and between fourth to seventh day in cases of haemorrhage. Lieberman et al. (1957) could detect raised levels of C.S.F. enzymes in a case even on fifteenth day. Brodeli et al. (1959), however, reported significant rise in serum and C.S.F. enzyme levels during the first ten days. Laha and Bhargava (1964) reported normal values by tenth day of the onset of illness. Mathur et al. (1965) found that the raised levels returned to normal by the twelfth day. Davies Jones (1970) reported normal values in his series of patients examined 5 weeks after the episode. Singh et al. (1972) observed a declining trend in the enzyme levels but the levels did not touch normal even after tenth day. Similar were the findings of Kohli et al. (1978). Kaul et al. (1978) reported high levels of cerebrospinal fluid S.G.O.T. persisting even up to third week after the onset.

Significantly higher values were obtained in cases of cerebral haemorrhage as compared to infarction. Similar findings have been reported by Singh et al. (1972) Kaul et al. (1978) and Kohli et al (1978). However, Mathur et al. (1965) reported highest enzyme values in cases of subarachnoid haemorrhage rather than cerebral haemorrhage.

Laha and Bhargava (1964) could not report any significant difference in the degree of rise of enzyme activity between various types of cerebrovascular accidents.

The higher C.S.F. G.O.T. values in cerebral haemorrhage could be due to more extensive cortical damage in cerebral haemorrhage than elsewhere. Admixture with blood may have further added to higher cerebrospinal fluid G.O.T. values.

(b) Lactic Dehydrogenase :

In the present study cerebrospinal fluid L.D.H. levels were significantly elevated in both the groups of cerebrovascular disease, infarction as well as haemorrhage ($P < 0.001$). These findings are in conformity with those of Fleischer et al (1957), Wroblewski et al. (1957), Jakoby and Jakoby (1958), Green et al. (1958), Wolintz et al. (1969), Bedi et al. (1974), and Chaudhri et al. (1976). Wroblewski et al (1958) on the other hand, reported normal cerebrospinal fluid L.D.H. levels in majority of cases of cerebral thrombosis. There was no correlation between C.S.F. and serum L.D.H. Similar findings have been reported by Wolintz et al. (1959) and Bedi et al. (1974). The rise in cerebrospinal fluid L.D.H. levels in cases of cerebrovascular diseases may be due to the following factors :

1. Release of the enzyme from the infarcted tissues (or anoxic areas).

2. Release from the degraded extravasated blood in cases of haemorrhagic lesions.

Peak levels of cerebrospinal fluid L.D.H. were obtained within the first three days of the onset of illness in infarction as well as haemorrhage. Jakoby and Jakoby (1959) reported that levels may be low soon after symptoms appear and increase only after some days. Wroblewski et al (1958) reported maximum activity within one to three days. Similar were the findings of Welints et al. (1969). In cases of cerebral haemorrhage the peak levels were obtained on first day by Chaudhri et al. (1976).

The differences in the time of peak enzyme activity may be accountable by the fact that the time of removal of C.S.F. may vary in each series. Also the extent of damage produced, too, may alter the results.

Cerebrospinal fluid L.D.H. levels were significantly higher ($P < 0.001$) till last followup in cases of infarction as well as haemorrhage. Wroblewski (1959) reported that cerebrospinal fluid L.D.H. levels returned to normal by fifth to tenth day. Sedi et al (1974) reported that C.S.F. enzyme values came to normal after three weeks in patients who survived.

Comparatively extremely high cerebrospinal fluid L.D.H. levels were found in haemorrhage as compared to infarction ($P < 0.001$). This in conformity with findings of Wroblewski et al (1958) who reported sizeable

increments in cerebrospinal fluid L.D.H. in haemorrhage. Similar findings were reported by Wolintz et al. (1969), Bedi et al. (1974) and Chaudhri et al. (1976). Higher values of cerebrospinal fluid L.D.H. in haemorrhage could be due to :

1. Greater parenchymal damage in haemorrhagic lesions.
2. Concomitant admixture of C.S.F. with blood, which further raises the cerebrospinal fluid L.D.H. enzymatic activity.

(c) Enzyme levels and prognosis :

On comparison of mean peak C.S.F. enzyme levels between improved and expired cases of diagnostic groups, interesting findings emerged. Significantly higher cerebrospinal fluid G.O.T. and L.D.H. values were found in cases who expired in comparison to improved ones ($P < 0.001$ and < 0.01 respectively, Table-XXII). Regarding cerebrospinal fluid G.O.T. similar views have been expressed by Singh et al (1972), Kaul et al (1978) and Kohli et al. (1978). Wolintz et al. (1969), Bedi et al (1974) and Chaudhri et al. (1976) have observed similar increments in cerebrospinal fluid L.D.H. and related them to worsening of prognosis.

Higher values were found in deteriorating patients and expired cases. This may be chiefly due to the greater extent of cellular damage produced in such cases. Brodali et al. (1969) also have reported that significant elevations

for C.S.F. enzymatic activity occured only with patients suffering from large infarcts.

When serum G.O.T. levels were compared it was found that significant differences existed between improved and expired cases in case of haemorrhagic lesions only ($P < 0.001$). It may be that in haemorrhagic lesions the higher serum G.O.T. activity (as compared to infarction) raises the sensitivity of this estimation.

(d) Diagnostic significance of Enzyme Levels :

Maximum C.S.F. enzyme levels (G.O.T. and L.D.H.) were found in cases of haemorrhagic lesions. Similar have been the findings of Singh et al (1972), Bedi et al (1974), Chaudhari et al (1976), Kohli et al (1978,81) and Kaul et al. (1978). However, the above findings are at variance with the observation of Laha and Bhargava (1964) who did not report any variation in enzyme levels between various cerebrovascular accidents. No critical diagnostic levels could be obtained in this work. Kaul et al (1978) reported similar findings. Significantly higher values of serum G.O.T. were obtained in cerebral embolism as compared to thrombosis ($P < 0.05$). Due to small number of cases, it is difficult to deduce any conclusion from this. C.S.F. enzyme levels (G.O.T. and L.D.H.) were however, insignificant on comparision.

Highly significant differences in cerebrospinal fluid G.O.T. and serum G.O.T. ($P < 0.001$) were obtained on comparing subarachnoid haemorrhage to cerebral haemorrhage.

No significant differences in cerebrospinal fluid L.D.H. could be found ($P > 0.01$).

Higher values in cerebral haemorrhage may be in part due to greater parenchymal damage present in such cases along with the contribution of contamination by blood.

C.S.F. AND SERUM ENZYME LEVELS IN MENINGITIDES :

(a) Tuberculous meningitis :

All cases showed a significant elevation of cerebrospinal fluid G.O.T. and L.D.H. from the time of admission ($P < 0.001$). Peak levels were obtained on admission itself and showed on decline thereafter, but were statistically significant during second week also. Rise in cerebrospinal fluid G.O.T. has been reported also by Green et al. (1957).*

* Aronson (1961), Srivastava et al. (1971), Reddy et al. (1972), and Khanna et al. (1977). Our findings are at variance with those of Shirole and Nair (1974) and Praharaj (1979) who reported normal C.S.F. G.O.T. levels in cases of tuberculous meningitis. In the present study serum G.O.T. and L.D.H. were found to be normal in both varieties of meningitis. This may be because of lack of cellular damage in these cases. Out of 8 cases who improved, 3 showed sequelae in the form of lateral rectus palsy, optic atrophy and right sided hemiparesis. However, enzyme levels of cerebrospinal fluid G.O.T. and L.D.H. in these 3 were statistically insignificant as

compared to enzyme levels in rest of the improved cases ($P > 0.5$). No critical prognostic levels could be ascertained.

On comparing mean peak cerebrospinal fluid G.O.T. and L.D.H. levels between improved and expired cases significant difference was found in cerebrospinal fluid. G.O.T. levels ($P < 0.05$). Cerebrospinal fluid L.D.H. levels did not show any significant difference ($P > 0.05$). Therefore in the present study cerebrospinal fluid L.D.H. levels did not vary with the ultimate clinical outcome of the cases of tuberculous meningitis, whereas higher cerebrospinal fluid G.O.T. levels were associated with a bad prognosis. Cerebrospinal fluid G.O.T. levels were not found to be of distinct diagnostic significance in a proper clinical setting. However cerebrospinal fluid L.D.H. levels were quite higher (91.0 ± 41.3 I.U./L). This finding is in agreement with the observation of Khanna et al (1977) who said that cerebrospinal fluid L.D.H. levels could be of help in diagnosing controversial cases of tuberculous meningitis with inconclusive C.S.F. findings. C.S.F. enzyme values showed a falling tendency on the subsequent follow up. This could serve as a guide to success of therapy. Similar were the findings of Wroblewski et al. (1958) and Feldman et al. (1975).

No correlation between C.S.F. enzyme levels of G.O.T. and L.D.H. with cell count or protein levels could be found. Similar findings have been reported by Khanna

et al. (1977) and Hallock et al. (1978).

(b) Pyogenic meningitis :

Cerebrospinal fluid G.O.T. and L.D.H. levels were significantly raised ($P < 0.001$) in all the ten cases of this illness, from the time of admission. Highest enzyme values were obtained on admission and a significant level above the normal was present on first followup. The above findings are in consonance with those of Wrobleu-ski (1957, 58), Aronson (1960), Lending et al. (1964), Beaty et al. (1968), Neches and Platt (1968), Reddy et al. (1972), Shirole and Nair (1976), Feldman et al. (1975), Hallock et al. (1978), Praharaj et al. (1978) and Gupta et al. (1982). No changes in serum G.O.T. and L.D.H. levels could be detected.

Extremely high mean peak C.S.F. enzyme levels were obtained in this group.

On comparing mean peak cerebrospinal fluid G.O.T. and L.D.H. levels between improved and expired cases significant variations in enzyme levels were found ($P < 0.05$ and < 0.001 respectively). However on comparing individual cases, Out of 10 patients there were four expired cases. Fifty percent of them had cerebrospinal fluid G.O.T. values between 15 - 30 I.U./L. and rest had values above 30 I.U./L. Two out of four expired cases had cerebrospinal fluid L.D.H. values between 150 - 200 I.U./L. and rest had values more than 200 I.U./L.

Higher values of cerebrospinal fluid G.O.T. and L.D.H. are therefore related to a bad prognosis. Similar findings have been reported by Reddy et al. (1972), Beaty et al. (1968), Belsey (1969) and Gupta et al. (1982). Shirole and Nair (1974), however could not correlate cerebrospinal fluid G.O.T. levels with course and prognosis of the disease.

The enzyme levels fall with therapy to lower values on subsequent followup. Cerebrospinal fluid L.D.H. levels serving as an index to success of therapy in pyogenic meningitis have also been reported by Wroblewski et al. (1958) and Feldman et al. (1975).

Extremely high cerebrospinal fluid L.D.H. values were obtained in all cases of pyogenic meningitis. Similar findings have been reported by Beaty et al. (1968). Hallock et al. (1978) has suggested that evaluation of cerebrospinal fluid L.D.H. may help in the diagnosis of culture riegative pyogenic meningitis.

No correlation between cerebrospinal fluid G.O.T. and L.D.H. values and cell count and protein content of C.S.F. could be achieved. A relationship between cerebrospinal fluid G.O.T. levels and protein content of C.S.F. has been observed by Miyazaki et al. (1958), Srivastava et al. (1971) and Reddy et al. (1972). Shirole and Nair (1974) observed an association of cerebrospinal fluid G.O.T. levels with cellular content of C.S.F. A semiquantitative relation of leucocyte count with cerebro-

spinal fluid L.D.H. in pyogenic meningitis was reported by Wrobiewski (1958). However no such relationship was reported by Katzman et al. (1957), Beaty et al. (1960) and Neches and Platt (1968). Findings in the present study are similar to those of latter group of workers.

THE MISCELLANEOUS GROUP :

(a) Transient ischaemic attacks :

Out of three patients of transient ischaemic attacks, none showed any variation of serum or C.S.F. enzyme levels. These findings are in conformity with those of Lieberman et al. (1957) who contended that mild or transient episodes of cerebrovascular insufficiency did not cause elevations of G.O.T. activity in serum. Similar observations in C.S.F. or serum have been reported by Mathur et al. (1965), Davies Jones (1970) and Singh et al. (1972). The normal levels of both enzymes in C.S.F./serum could be due to absence of frank cellular damage in these cases.

(b) Cortical vein thrombosis :

Statistically significant elevations of G.O.T. and L.D.H. were observed in the two cases studied under this group. No change was observed in serum levels. Higher serum and C.S.F. G.O.T. levels have also been reported by Singh et al. (1972), Kohli et al. (1978) reported raised cerebrospinal fluid G.O.T. levels in their three cases. However Kaul et al. (1978) reported that C.S.F. G.O.T. levels in their three cases were within normal limits. The

lack of studies on a sizeable number of patients under this group prevents one from further comments on these patients.

(c) Encephalitis :

Encephalitis was diagnosed in three patients. None of them had any significant alteration in serum/ C.S.F./S.G.O.T./L.D.H. levels. Similar findings have been reported by Myerson et al. (1957), Lending et al. (1964) and Gupta et al. (1982).

Beaty et al. (1968) found slight elevations in cerebrospinal fluid L.D.H. in viral infections of the nervous system. The normal levels of enzymes could be of value in differentiating this group from other types of meningitides where C.S.F. reports are inconclusive (e.g. partially treated meningitis of any aetiology).

SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

The present study was carried out on 58 patients of acute neurological episodes including 16 cases of cerebral infarction, 12 each of intracranial haemorrhage and tuberculous meningitis, 10 of pyogenic meningitis and 8 with miscellaneous conditions. Twenty age and sex matched individuals served as controls. Serial serum and cerebrospinal fluid (C.S.F.) glutamic oxaloacetic transaminase (G.O.T.) and lactic dehydrogenase (L.D.H.) estimations were done in the control and study groups. Following conclusions could be drawn from the study :

1. Mean cerebrospinal fluid G.O.T. and L.D.H. levels in controls were 5.5±2.5 I.U./L and 16.2±4.9 I.U./L respectively.
2. Mean serum G.O.T. and L.D.H. levels in controls were 9.85±4.6 I.U./L and 94.25±38.6 I.U./L respectively.
3. Statistically significant elevations of serum G.O.T. and cerebrospinal fluid G.O.T. and L.D.H. were found in all cases with infarction and haemorrhage (Serum G.O.T. : $P < 0.05$ and < 0.001 in infarction and haemorrhage respectively. C.S.F. G.O.T., L.D.H. : $P < 0.001$ in both groups).
4. Cerebrospinal fluid G.O.T. and L.D.H. showed a more marked rise in haemorrhage than in infarction (< 0.001), the values of both enzymes being maximum on the first estimation.

5. Serum G.O.T. showed maximum activity between fourth to seventh day in infarction and between first to third day in haemorrhage.

6. None of the enzyme levels returned to normal till the last follow up.

7. Significant differences between mean peak levels of G.O.T. and L.D.H. in C.S.F. were found between improved and expired cases in infarction as well as haemorrhage ($P < 0.001$ and < 0.05 for G.O.T. and L.D.H. levels respectively in both groups). S.G.O.T. levels showed significant difference between improved and expired cases only in cases with haemorrhage ($P < 0.001$).

8. No definite diagnostic levels (cut off levels) of C.S.F. G.O.T./L.D.H. could be obtained in demarcate embolism from thrombosis ($P > 0.1$). Serum G.O.T. values, however, showed a significant difference ($P < 0.05$) in these groups. C.S.F. and serum G.O.T. showed significant difference ($P < 0.001$) between subarachnoid and cerebral haemorrhage unlike cerebrospinal fluid L.D.H. ($P > 0.01$).

9. Cerebrospinal fluid G.O.T. and L.D.H. were significantly ($P < 0.001$) raised in both tuberculous and pyogenic meningitis, the values in the latter being markedly higher ($P < 0.001$). Serum levels of both enzymes were normal.

10. Peak levels of both enzymes were obtained on first estimation.

11. Enzyme levels continued to remain significantly higher ($P < 0.001$) than normal till the last follow up.

12. Significant differences in cerebrospinal fluid G.O.T. levels between improved and expired cases of both types of meningitides (Tuberculous and pyogenic) were found ($P < 0.05$ and < 0.001 respectively), while cerebrospinal fluid (L.D.H.) showed significant difference only in pyogenic meningitis ($P < 0.001$).

13. No definite diagnostic levels (cut off levels) could be obtained between tuberculous and pyogenic meningitis though G.O.T. and L.D.H. values in C.S.F. were significantly higher in pyogenic meningitis as compared to tuberculous meningitis ($P < 0.001$).

14. There was no significant correlation between C.S.F. enzyme values and routine C.S.F. parameters, like cells and proteins ($P > 0.05$).

15. Significant C.S.F. G.O.T. and LDH elevations were found in both cases of cortical vein thrombosis; other enzyme levels in serum being normal. No enzyme change could be detected in other cases of the miscellaneous group.

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APPENDIX

CEREBROSPINAL FLUID ENZYMES IN ACUTE NEUROLOGICAL DISORDERS

Consultant Incharge : Dr. D.N. Mishra, M.D.
Name of investigator : Dr. Madhukar Mishra

Case No.

Patient's name : Age Sex :

Address : Ward/Bed No.

Occupation :

Socio-economic status :

Date of admission :

Date of discharge/Death :

Chief complaints :

Past history :

High fever Ear discharge
Cough with expectoration/Haemoptysis
Diarrhoea/vomiting
Hypertension
Diabetes
Myocardial infarction
T.I.A.
Coma
Convulsions
Paralysis

Personal history :

Smoker/nonsmoker
Vegetarian/non-vegetarian
Drinker/tetotaller

Family history :

Menstrual and obstetrical history :

Examination (General) :

Appearance Pulse
Built B.P.
Anaemia R/R
Cyanosis

Jaundice
Clubbing
Oedema
Lymph nodes
Hydration

Temperature
Skin pigmentation

Systemic Examination :

C.V.S.

Respiratory :

Abdomen :

Loco motor :

Spine :

C.N.S :

Higher psychological functions :

Sensorium

Appearance and behaviour

Emotional state

Delusions and hallucinations

Orientation in place, time and person

memory

Speech :

Dysarthria

Aphasia

Cranial nerves :

	R	L		R	L
I			VII		
II			VIII		
III			IX		
IV			X		
V			XI		
VI			XII		

Pupils :

Motor system	R/U	R/L	L/U	L/L
Bulk				
Power				
Tone				
Coordination				
Gait				
Involuntary movements				

Sensory system :

Tpuch
Pain
Temperature
Pressure
Vibration
Joint sense
Position
Cortical

Reflexes :

		R	L
Deep	AJ		
	KJ		
	BJ		
	TJ		
	SJ		
	JAW		

Superficial :

Corneal
Abdominal
Cremasteric
Plantars

Extrapyramidal signs :

Signs of meningeal irritation :

NR
KS
BS

Spine, Skull, Posture :

Cutaneous, Naevi/Bruits in neck :

Investigation :

Blood - TLC
DLC
Hb
ESR

Fundus
ECG
CSF Cytobio

Urine- Albumin
Sugar
M/E

	CSF	Serum
Blood sugar	SGOT	SGOT
Urea	LDH	LDH
Cholesterol		
VDRL		

Diagnosis :